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COEXISTENCE PHENOMENA IN THE CRITICAL REGION

V. THE GRAVITY EFFECT IN THE BINARY LIQUID SYSTEM ANILINE-CYCLOHEXANE FROM LIGHT SCATTERING[1]

F. E. MURRAY[2] AND S. G. MASON

ABSTRACT

Transmittance measurements were used to investigate vertical concentration gradients, at temperatures slightly above the critical, in a binary liquid system. The gradients, which are predicted theoretically, did not begin to form during time intervals of several hours. It was found that a theoretical relation between transmittance and concentration gradient did not apply, even qualitatively, to the results obtained. The significance of these observations is discussed.

INTRODUCTION

In previous publications (3, 4), the authors reported large vertical gradients in density near the liquid–vapor critical point in one-component systems. These gradients, due to gravitational compression, were anticipated owing to the large compressibility of a fluid in the critical region.

The case of vertical concentration gradients in a binary liquid system, at temperatures slightly above the critical, forms an analogue which is not so obvious. It was, however, shown by Yvon (9) that such concentration gradients are predicted theoretically. Since Rice and Rowden (6) reported a flat apex on the coexistence curve for aniline–cyclohexane, it was of interest to see if this flat top could be ascribed to concentration gradients by analogy to the gravity effect in one-component systems (3, 4, 7, 8).

The critical solution point for a binary liquid system is defined by the conditions

$$[1] \qquad (\partial\mu_1/\partial c_1)_{T,P} = (\partial^2\mu_1/\partial c_1^2)_{T,P} = 0,$$

where μ_1 and c_1 are respectively the chemical potential and mole fraction of component 1 in the solution.

For the variation of concentration with height in a binary liquid mixture, Yvon (9) obtained an expression which may be simplified to the form

$$[2] \qquad (\partial c_1/\partial x)_T = G(x)/(\partial\mu_1/\partial c_1)_{T,P},$$

where x is distance measured positive downward and $G(x)$ is a finite function of x. From Equation [2], Yvon concluded that when the solution approaches the critical state, i.e. when $(\partial\mu_1/\partial c_1)_{T,P} \to 0$, $(\partial c_1/\partial x)_T$ becomes very large.

[1]*Manuscript received November 1, 1957.*
Contribution from the Department of Chemistry, McGill University, Montreal, Quebec.

[2]*Holder of a Fellowship from the National Research Council of Canada. Present address: British Columbia Research Council, University of British Columbia, Vancouver, B.C.*

It was considered that the light-scattering coefficient, which is highly sensitive in the critical region, might be used to reveal experimentally the composition gradients. Following the work of Einstein (1), the turbidity in a binary liquid system is given by the expression

$$[3] \qquad \tau = B\bar{V}_1 c_2 (\partial\epsilon/\partial c_2)^2/(\partial\mu_1/\partial c_1)_{T,P},$$

where B is a constant at any temperature and wave length of the incident light, $\bar{V}_1$ is the partial molar volume of component 1, ϵ is the optical dielectric constant of the fluid. By combining Equations [2] and [3] the variation of concentration with height becomes

$$[4] \qquad (\partial c_1/\partial x)_T = B'G(x)\tau.$$

B' is a constant for any given concentration, temperature, and wave length of the incident light. Equation [4] is analogous to the relationship between turbidity and density gradient in a one-component system near the gas/liquid critical point.

Equation [2] predicts large vertical gradients in concentration when $(\partial\mu_1/\partial c_1)_{T,P}$ becomes very small at temperatures slightly above the critical. Equation [4] predicts that the magnitude of these gradients, at any height in the fluid column, will be directly proportional to the turbidity.

The following symbols are used to denote measured quantities:

T = temperature in degrees centigrade,
T_f = the value of T at which visible droplets form when the fluid is cooled slowly,
T_c = the highest value of T_f observed,
$\Delta T = (T - T_c)$,
V_1 = the volume fraction of aniline in the binary mixture,
I_0 = the intensity of the incident light,
I = the intensity of the transmitted light,
$\tau = 2.30 \log I_0/I$.

EXPERIMENTAL

Apparatus

The essential details of the apparatus have already been described (3, 4). In the present experiments, only the methods of filling and changing the composition of the fluid were altered.

To facilitate changing the composition of the system, the device illustrated in Fig. 1 was attached to the valve V_2 (the connection between V_2 and the bomb is illustrated in Fig. 1*a* of Reference 3). In Fig. 1, the double line denotes glass tubing and the single line metal; the open side of the valve V_5 was attached to a vacuum system. With the pinch-clamp y open and the tubing from the mercury surface to V_2 filled with cyclohexane, liquid could be forced into the bomb by opening valve V_2.

Procedures

The cyclohexane was purified by distillation from silica gel. Merck's reagent grade aniline was dried for 5 days over KOH and then fractionated. The sample fraction was collected in a glass bulb, which was sealed to valve V_2 (Fig. 1) with a Kovar glass-to-metal seal.

The aniline sample was degassed under vacuum and then forced, by mild heating, into the evacuated bomb under its own vapor pressure. The initial amount of cyclohexane was introduced in the same manner until the volume fraction of aniline was

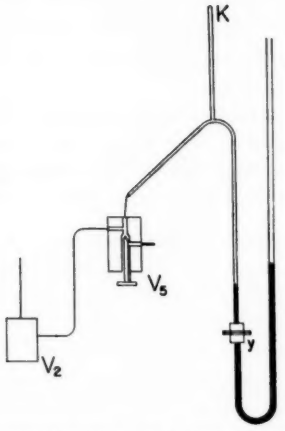

FIG. 1. Auxiliary filling system used for adding cyclohexane to the system aniline–cyclohexane.

0.416. With this initial filling, the liquid column in the bomb was about 30 cm. long.

The composition of the binary mixture was changed by allowing cyclohexane to enter the bomb by opening valve V_2 (Fig. 1). This was possible since the vapor pressure in the bomb was about 150 mm. of mercury, while the cyclohexane in the filling device was at atmospheric pressure. Volume fractions were obtained by measuring the length of the fluid column in the bomb. This procedure, which assumed no volume change on mixing, was considered sufficiently accurate for the purposes of this experiment.

RESULTS

Coexistence Curve

The curve bounding the region of two discrete phases (lower diagram, Fig. 2) was obtained by observing the first formation of visible droplets when the liquid mixture

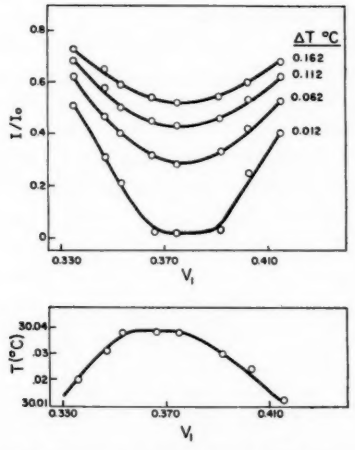

FIG. 2. The variation of optical transmittance with volume fraction of aniline at a number of temperatures above T_c (upper diagram). The coexistence curve for aniline–cyclohexane at the vapor pressure of the fluid system (lower diagram).

was cooled very slowly. The observed value of T_c was $30.04 \pm 0.02°$ C., which is slightly higher than the value 29.63° C. reported by Rice and Rowden (6). T_c was observed at three values of V_1; however, the apex of the curve could be drawn either flat or rounded within the limits of experimental error.

At T_f, the appearance of droplets occurred uniformly throughout the length (approximately 30 cm.) of the fluid column. The initial fog of condensation did not form at a particular level in the bomb, as was observed in one-component systems (3, 4, 8). This indicates that a vertical concentration gradient did not exist.

The Variation of Transmittance with Volume Fraction

The upper diagram in Fig. 2 shows the variation of optical transmittance (I/I_0) with volume fraction of aniline. The almost flat portion at the minimum of the curve at $\Delta T = 0.012°$ C. is probably due to insensitivity of measurements at this very low value of the transmittance. At all other values of ΔT, the transmittance–composition isothermals are smooth curves which pass through a minimum at a value of V_1 at which the phase volumes are equal at T_c. These isothermals are of the same form as those obtained by Zimm (10) for the binary liquid system perfluoromethylcyclohexane – carbon tetrachloride.

The Variation of Transmittance with Height

No vertical gradients in transmittance formed over periods of several hours after cessation of stirring at any value of V_1 and at various temperatures down to $\Delta T = 0.012°$ C. Since, at constant temperature, transmittance varies with composition as shown in Fig. 2 (upper diagram), it follows that no concentration gradients were formed. This was unexpected.

No extensive time-lag phenomena were observed in the binary liquid system such as were found in one-component systems near the critical point (5). When the binary liquid column, above T_c, was stirred, prestirring values of the optical transmission were re-established within 5 minutes after cessation of stirring. This time was of the order required for establishment of thermal equilibrium after the fluid had been heated by the viscous work of stirring.

The Variation of Turbidity with Temperature

Fig. 3 shows the variation of the inverse of the turbidity τ with temperature at positive values of ΔT. Results obtained for the one-component systems ethylene and xenon (4) are included for comparison.

The higher turbidities observed for the aniline–cyclohexane system show a linear dependence of τ^{-1} on ΔT right down to $\Delta T = 0$. Zimm (10) reported a similar dependence of turbidity on temperature for the system perfluoromethylcyclohexane – carbon tetrachloride.

The Effect of Radiant Energy

The action of the polychromatic light beam in passing through the fluid column caused no noticeable effect on the turbidity of one-component systems. Above T_c, in the aniline–cyclohexane mixture, the light beam caused the turbidity to slowly decrease. After about 10 minutes at a fixed level, a relatively clear path through the turbid fluid was visible at the point where the light beam had been; on moving the light source, this region of relative transparency disappeared within several minutes. The phenomenon was very pronounced at small values of ΔT. This type of behavior seems to

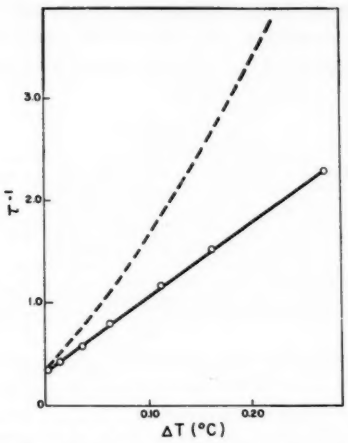

FIG. 3. Variation of the inverse of the turbidity with ΔT at the critical composition in the system aniline–cyclohexane (solid line). The broken line shows the results obtained for ethylene and xenon under similar conditions.

correspond to that observed in disperse systems, which is called "photophoresis" (2). To minimize the effect of this phenomenon on the transmission measurements, observations were recorded immediately after moving the light source. This effect is worthy of further investigation.

DISCUSSION

Since no concentration gradients are formed in the system aniline–cyclohexane at temperatures slightly above T_c, it seems that the flat apex observed by Rice and Rowden (6) on the coexistence curve for aniline–cyclohexane could not be caused by the effect of gravity. This is in contrast to the behavior in one-component systems where the flat-topped coexistence curve, observed by several authors, can be explained in terms of density gradients (4, 7, 8).

Failure to observe the gradients predicted by Equations [2], [3], and [4] may indicate that the theoretical homophase model, used in the derivation of these equations, is inadequate to describe conditions in the region of the critical solution point. Previous observations (5) indicated that molecular clusters, formed at temperatures slightly above T_c in one-component systems, have appreciable lifetimes and it may be more realistic in both cases to treat the clusters as droplets of another phase.

It must be realized that, at temperatures slightly below the classically-defined critical temperature, the difference in density and the interfacial tension between the two phases become so small that a dispersion of the two phases could be extremely stable. It may well be that the temperature T_c, now accepted as the critical temperature, is in reality the minimum temperature at which the two existing phases, of critical composition, will form a stable dispersion of minute droplets when the difference in density and the interfacial tension between the two phases have reached a very low value.

The classically-defined critical temperature, at which the difference in density and the interfacial tension between the two phases actually become zero, would be somewhat higher and could not be detected visually. It would, in fact, be extremely difficult to

detect the temperature corresponding to the classically-defined critical point owing to the continuous nature of the transition. In view of the above considerations, it may be better to refer to the temperature T_c, presently accepted as the critical temperature, as the "critical dispersion temperature".

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PHOTOOXIDATION OF KETONES IN AN O^{18} ENRICHED ENVIRONMENT[1]

J. R. DUNN[2] AND K. O. KUTSCHKE

ABSTRACT

A technique is described in which the origins of the products of photooxidation of ketones can be obtained in respect to whether they arise from the carbonyl or the alkyl groups of the ketone molecule. This is accomplished with the use of reactant molecular oxygen which has been enriched in the O^{18} isotope. Application of this to the photooxidation of acetone indicates that a large fraction of the carbon dioxide contains the carbonyl group of the ketone and that acetyl radicals play an important role in the oxidation to temperatures at least as high as 175° C. Propionyl radicals are much less stable, and, in the photooxidation of diethyl ketone, their reactions, other than decomposition, appear to be negligible at quite low temperatures. Some comment is made on the mechanisms of these photooxidations.

In the course of recent work on the photooxidation of azomethane it was observed that relatively small amounts of the oxides of carbon were produced (1). In particular, it has been suggested (1) that, under the conditions used in these experiments, methyl radicals are not oxidized to carbon dioxide to any large extent and that the greater amounts of the dioxide found in the photooxidation of acetone (2) must have arisen from an oxidation of the carbonyl group. Such an oxidation might occur, for example, by reactions of acetyl radicals (3) or acetonyl radicals (1) with oxygen. This disagrees with the work of Christie (4), who observed that essentially all of the carbon dioxide was radioactive when produced in the photooxidation of $C^{14}H_3COC^{14}H_3$. In view of this contradiction and of the impure acetone sample used by Christie (some unidentified material which led to unexpectedly large yields of carbon dioxide (4)), it was thought worth while to check the result by an independent method.

If oxygen enriched in O^{18} is used in these experiments, any carbon dioxide containing the methyl carbon atom will show the same O^{18} enrichment as does the reactant oxygen. Conversely, if the carbonyl group is the source of the dioxide and if it is assumed that the carbonyl group survives the reaction without rupture of the C—O carbonyl linkage, the carbon dioxide produced will show only one-half the enrichment of the reactant oxygen. By a similar argument, carbon monoxide which arises from the carbonyl group, for example by the decomposition of acetyl radicals, will possess the natural isotopic composition, while that which is formed from the terminal carbon atom will be enriched to the same extent as is the reactant oxygen. Similar considerations show that formaldehyde that arises from the carbonyl group will have the natural abundance of O^{18}, while that arising from methyl radical oxidation will be enriched.

The carbon monoxide observations also aid in the investigation of the primary products of ketone photolysis. It seems well established that methyl and acetyl radicals are the first radicals produced from the excited acetone molecule formed by light absorption at ~3130 Å (5). Acetyl radicals so formed are energy rich, and a certain fraction of them are thought to decompose before experiencing any significant number of collisions. The remainder react as acetyl radicals, the predominant reaction being decomposition into carbon monoxide and a methyl radical presumably by a quasi-unimolecular process (6), so that

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Φ_{CO} is temperature dependent. General confirmation of this is found in the observations made here, which indicate that the extent of decomposition of the acetyl radical varies with temperature at a given oxygen pressure.

An analogous argument may be made in the case of diethyl ketone photooxidation in which the primary process is thought to differ only in degree from that in acetone (7). Substantiation for such a view may be deduced from the data presented here.

Only preliminary results appear here; more detailed investigations are reported in forthcoming publications from these laboratories. Since this work was completed, the results of Taylor and Blacet (8) appeared; these authors presented a similar treatment of biacetyl photooxidation.

EXPERIMENTAL

Experimental procedures were similar to those used previously in these laboratories (1) with a few exceptions. The reaction cell together with a magnetically driven stirrer was housed in a thermostatted air oven. A few centimeters of 8 mm. tubing were external to the oven and connected via glass float-valves to a mercury cutoff, leading to the storage and analytical systems, and to a small Toepler pump which served to "dose" oxygen into the reaction system as required to maintain the oxygen pressure constant to within some 10–15%. The system appeared to prevent the polymerization of formaldehyde during exposure since reproducible recoveries from the LeRoy still (9) were achieved for this product. The carbon monoxide – oxygen fraction, removed at −196° C., was slowly introduced into a vessel containing a fresh surface of yellow phosphorus. With sufficiently slow introduction negligible oxidation occurred; blank experiments showed no exchange during this procedure. Carbon monoxide recovered was submitted for mass spectrometric analysis. The carbon dioxide fraction, separated at −160° C., was submitted for mass analysis with no further treatment; small amounts of formaldehyde were always present. The bulk of the formaldehyde was recovered with prolonged pumping at −130° C. and submitted for isotopic analysis. Higher-boiling compounds were not investigated in the work reported here.

Analogous procedures were used with diethyl ketone; formaldehyde was absent but acetaldehyde was a major product. Some C_2 hydrocarbon was also found.

Acetone and diethyl ketone were good quality commercial products, carefully dried and outgassed. Oxygen was obtained from the slow electrolysis, *in vacuo*, of about 1 cm.^{3} of outgassed, enriched water (from Dr. L. C. Leitch of these laboratories) using a drop of sulphuric acid as an electrolyte. The oxygen was led over platinized asbestos at 300° C., and then through several liquid nitrogen traps to storage. Mass spectrometric analysis yielded a 34/32 ratio 2.90×10^{-2} (natural 0.34×10^{-2}) indicating that 2.8% of the oxygen molecules contained an atom of O^{18}. The same procedure was followed with water stated to contain 10.17% O^{18} (Dajac Laboratories); analysis of the oxygen gave 9.59 atom % O^{18}. Only a few experiments, not reported here, were made with the more highly enriched oxygen; they were in essential agreement with the results reported.

RESULTS AND DISCUSSION

With conditions of acetone and oxygen pressures, absorbed light intensity, and temperature similar to those used by earlier workers (2, 4, 10), over-all quantum yields for the production of the oxides of carbon and for the consumption of oxygen were in excellent agreement. However, the fraction of the total carbon monoxide produced which contains the carbonyl group, x_1, varies with temperature and oxygen pressure as shown in Table I.

TABLE I

ORIGIN OF THE OXIDES OF CARBON IN KETONE PHOTOOXIDATION

	O_2 (mm.)	x_1	x_2	x_3
Acetone[a]				
120° C.	0.08	0.25	0.92	
	0.17	0.22	0.92	
	0.3	0.18	0.94	
	0.5	0.0	0.83	
175° C.	0.08	0.73	0.88	
	0.56	0.12	0.82	
	0.99	0.43	0.80	
	2.0	0.12	0.80	
	14	—	0.81	
Diethyl ketone[b]				
120° C.	0.33	0.87	0.79	0.52
	0.84	—	0.79	—
	1.6	0.90	0.90	0.56
175° C.	0.4	0.88	0.74	0.32
	0.7	0.89	0.69	0.29
	1.3	0.77	0.55	0.29

[a] *Ketone pressure 13 cm.;* $I_a \sim 2 \times 10^{12}$ *quanta cm.*$^{-3}$ *second*$^{-1}$*;* $\lambda \sim 3130$ Å*;* $\sim 0.5\%$ *decomposition.*

[b] *Ketone pressure 3.5 cm.;* $I_a \sim 1 \times 10^{12}$ *quanta cm.*$^{-3}$ *second*$^{-1}$*;* $\lambda \sim 3130$ Å*;* $\sim 1\%$ *decomposition.*

The trend, aside from one experiment at 175° C., indicates that even at these temperatures acetyl radical lifetime is sufficiently long to allow a reaction with oxygen which apparently does not produce carbon monoxide. This is in agreement with the observations of McDowell and Thomas (11), who observed that acetyl radicals reacted with oxygen, rather than decomposed, as high as 200° C.

Only a small fraction $(1-x_2)$ of the carbon dioxide ever arises from the methyl group (Table I). It is felt that this conclusion is more reliable than that reached by Christie (4) in view of the uncertainty, mentioned earlier, in the latter work. Moreover, it agrees with the observation that, in the absence of carbonyl groups in the substrate molecule, carbon dioxide is a minor product of methyl radical oxidation (1).

Attempts were made to determine the origin of the formaldehyde product by observing the 32/30 ratio in its mass spectrum. The results were inconclusive, however, since the 32 residual varied in an unpredictable manner whenever formaldehyde was present in the sample chamber.

Some experiments were done on the diethyl ketone photooxidation; the data are included in Table I. Absolute values of quantum yields were again in essential agreement with those of other workers (12, 13). Two experiments at room temperature yielded negligible amounts of carbon monoxide (other workers found $\Phi_{CO} \sim 0.1$ for similar conditions); the carbon dioxide from the room temperature experiments all contained the carbonyl group. The higher values for x_1 from diethyl ketone as compared to those from acetone at the same temperature and oxygen pressure presumably reflect the greater ease with which propionyl radicals decompose. Carbon dioxide could arise in part by mechanisms analogous to those suggested earlier for acetone, but at the higher temperatures a mechanism must exist which produces carbon dioxide from the ethyl group of the ketone. This conclusion is in harmony with the carbon-14 tracer data obtained by Finkelstein and Noyes (12). It is to be noted that the mechanism proposed by Jolley (13) does not take this fact into consideration. The origin of the acetaldehyde found here (x_3 is that fraction of the aldehyde which contains the carbonyl group of the ketone—see Table I)

cannot be explained simply. The present result disagrees with the conclusion of Finkelstein and Noyes (12), who found that essentially all the acetaldehyde arose from ethyl radical oxidation. No explanation can be offered for this disagreement. The possibility of exchange between acetaldehyde and reactant oxygen (mostly O^{16}) cannot be ruled out on the basis of present data.*

Much more data are obviously required before a consistent mechanism can be written for either of these photooxidations; tracer experiments are of particular importance. It is felt that the technique outlined here presents a means whereby such data may be obtained relatively simply since the enriched oxygen is readily prepared.

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We are indebted to the referee for drawing our attention to this point.

RADIOCHEMICAL ANALYSIS FOR LONG-LIVED FISSION PRODUCTS IN ENVIRONMENTAL MATERIALS[1]

W. F. MERRITT

ABSTRACT

A method is described whereby radiochemical analysis for the long-lived fission products Ru^{106}, Sr^{90}, Cs^{137}, and Ce^{144} may be performed on the same sample of soil, water, or biological material. Carriers are added and the material is fused at 550° C. with KOH, KNO_3, and K_2CO_3. Ruthenium and cesium are extracted with water, strontium and cerium remaining in the melt. Ruthenium is extracted into carbon tetrachloride as ruthenium tetroxide, cesium is absorbed on Duolite C-3 cation-exchange resin from alkaline solution, strontium and cerium are extracted from the melt with acid, cerium is precipitated as the hydroxide and strontium as the carbonate. The elements are precipitated, weighed, and counted according to standard procedures.

INTRODUCTION

Low-level radioactive wastes produced at Chalk River are disposed of from seepage pits in a carefully selected disposal area. In addition, sewage and other liquid effluent streams entering the Ottawa river may contain small but measurable quantities of radioactive material. It is necessary, therefore, to monitor the drainage basin of the disposal area and the Ottawa river below the plant site for any undesirable escape of radioactivity.

The movement of activity in the disposal area is followed by drilling wells and taking soil samples, by sampling the drainage water, and by taking specimens of vegetation and animals from the surrounding area. Activity in the river is monitored by continuous sampling of the project effluents and by taking samples of bottom muds, fish, clams, aquatic plants, etc. at regular intervals. The radioactive isotopes present and important from the public health point of view are the long-lived, high-yield fission products Sr^{90}, Ru^{106}, Cs^{137}, and Ce^{144}. Since Sr^{90} is readily absorbed into the body, is fixed in the bone, and has a long half-life and energetic radiation, it is considered the most hazardous of these radioisotopes.

An analytical method was desirable which could be applied to a wide variety of natural materials and which would detect very low concentrations of the isotopes listed above in the presence of substances occurring commonly in nature.

Analytical methods for these isotopes have been described by Coryell and Sugarman (1), by Meinke (2), and by Kleinberg (3). Crouch and Cook (4) have published an excellent detailed method of separation of a large number of radioisotopes. Kahn (5) has given detailed methods for the analysis of several isotopes adsorbed on soil using acid leaching for preliminary separation from the soil. However, we have found that, in particular, Cs^{137} could not be leached quantitatively from the typical sandy soil found at Chalk River. It has been shown (6) that the cesium ions are fixed in the interlayer positions of the layer silicate minerals, and thus it is necessary to destroy the silicate structure to release them.

Standard methods for decomposing silicates are of two general classes. The first involves heating with hydrofluoric and perchloric acid so that the silicon is volatilized as the tetrafluoride. In the second the material is fused with an alkali hydroxide, carbonate,

[1]*Manuscript received September 20, 1957.*
Contribution from Health Physics Branch, Biology Division, Atomic Energy of Canada Limited, Chalk River, Ontario.
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or peroxide. If the first method is used, ruthenium will be volatilized. In the second, the large amount of alkali added will interfere with standard cesium separations. Therefore, a different approach to the cesium analysis was needed.

Miller and Kline (7) first reported the ability of phenolic methylene–sulphonic-type cation-exchange resins to adsorb cesium from highly alkaline solutions. Ring (8) has adapted this method for separating cesium from large quantities of sodium. The method described here makes use of the ability of Duolite C-3* resin to effect a clean separation of as little as a milligram of cesium from gram quantities of potassium after alkali fusion.

PROCEDURES

Preparation of Samples

Water samples were evaporated to a few milliliters. Organic materials were wet ashed with nitric acid and hydrogen peroxide. Soil samples were ground to a fine powder with a mortar and pestle. Suitable quantities of material, determined by rough counting, were weighed or transferred into nickel crucibles, and standardized carrier solutions amounting to 20 mg. of strontium, cerium, and cesium and 10 mg. of ruthenium added by pipette. The mix was neutralized with dilute potassium hydroxide and dried under an infrared lamp. A fusion mixture of 2:1:1 by weight of potassium hydroxide, nitrate, and carbonate was added to the crucible to about 5–10 times the weight of the sample. The material was fused in a muffle at 550° C. for 2 hours, with the contents being swirled at 15-minute intervals. In this fusion the hydroxide and carbonate attack the silicate structure, and the nitrate oxidizes the ruthenium present to a soluble ruthenate. The melt was allowed to cool, and was leached twice with 10 ml. of water. The ruthenate and the cesium dissolve while the strontium and cerium remain in the melt as the insoluble carbonate and hydroxide.

Ruthenium

Potassium periodate (0.25 g.) was added to the solution to oxidize the ruthenate to ruthenium tetroxide. Zirconium, if present, will precipitate at this stage and can be removed by centrifuging. The solution was neutralized to a pH of 7 with 9 *M* sulphuric acid. Ten milliliters of redistilled carbon tetrachloride was added, and solvent extraction was started using an automatic "spitzer". The pH was reduced to 4 during the extraction by the dropwise addition of acid. Occasionally two extractions were necessary. The layers were separated and the ruthenium was stripped from the carbon tetrachloride with 6 *N* hydrochloric acid. The ruthenium was reduced to the metal with powdered magnesium as described by Kleinberg (3).

Cesium

The aqueous layer from the ruthenium solvent extraction was treated with saturated lithium hydroxide and the resulting precipitate of lithium carbonate was removed by centrifuging. A column of Duolite C-3, 60–100 mesh, 12×50 mm., was prepared in the lithium form by washing with 100 ml. of 0.5 *N* lithium hydroxide followed by 50 ml. of water. The sample solution was poured through the column and washed with 50 ml. of water. The column was then treated with 125 ml. of 0.5 *N* lithium hydroxide to elute the potassium. After a 50-ml. water wash, the lithium was eluted with 125 ml. of 0.2 *N* hydrochloric acid. The cesium was stripped off in 50 ml. of 6 *N* hydrochloric acid. Flow rates throughout were held to 2–3 ml./min.

**Chemical Process Company, Redwood City, California.*

The cesium solution was evaporated to 0.5 ml., made up to 3 ml. with water, and the cesium was precipitated with 2 ml. of 5% chloroplatinic acid.

Cerium

The solids from the original melt were treated with 10 ml. of 6 *N* nitric acid with heating. This solution was taken to dryness twice, with a few milliliters of concentrated nitric acid added, to dehydrate the silica. The dry mass was treated with 5 ml. of 6 *N* hydrochloric acid and two or three drops of 30% hydrogen peroxide to reduce any ceric ions to cerous, and the silica removed by centrifuging. The supernatant was diluted to 10 ml. and neutralized with ammonia gas to precipitate cerous hydroxide.

The cerium was then purified according to Kleinberg (3) by fluoride precipitation and by an oxidation–reduction cycle, oxidizing to Ce^{+4}, precipitating the cerium as ceric iodate, reducing to Ce^{+3}, and scavenging with zirconium iodate. The cerium was precipitated and weighed as the oxalate.

Strontium

After removal of the cerium as the hydroxide, strontium was precipitated by the addition of sodium carbonate. The precipitate was dissolved in 6 *N* nitric acid and the strontium was purified by two precipitations from fuming nitric acid. Calcium was removed by leaching the dried nitrate with alcohol–ether solution. Barium, if present, was removed by precipitation from alcoholic hydrochloric acid. The strontium salt was dissolved in water, scavenged with ferric hydroxide, and precipitated and weighed as the carbonate.

Counting

The precipitates were weighed and counted on standard 1-in. aluminum dishes. The counter used was a β scintillation counter, consisting of an anthracene crystal 1 in. in diameter and 10 thousandths of an inch thick, mounted on an RCA 6199 photomultiplier and covered with aluminized Mylar film. The unit was mounted in a 2-in. lead shield on a "Nuclear Chicago" model C110A* sample changer. The background of this system was 6 c.p.m., and the efficiency for $Sr^{90}+Y^{90}$ about 30%. The observed counting rates were corrected for background, for chemical yield based on added carrier, and for counter efficiency.

A typical set of results is shown in Table I.

TABLE I

TYPICAL RADIOCHEMICAL ANALYSIS OF DUPLICATE SAMPLES OF CONTAMINATED SOIL

Isotope	Weight of sample, mg., W	Weight of carrier, mg., A	Weight of ppt., mg., B	C.p.m. corrected for background, C	C.p.m. corrected for chemical yield, (A/B×C = D)	C.p.m. per g. of material, (D/W)×1000
Sr	24.5	18.7	12.1	50.0	77.3	3155
Sr	25.9	18.7	12.5	54.7	81.8	3159
Ru	24.5	9.9	6.6	9.4	14.4	588
Ru	25.9	9.9	7.9	10.8	13.5	522
Cs	24.5	20.1	17.2	19.6	22.9	935
Cs	25.9	20.1	15.9	17.4	22.0	850
Ce	24.5	23.2	14.7	23.2	36.6	1495
Ce	25.9	23.2	13.3	22.7	39.6	1529

**Nuclear Instrument & Chemical Corp., Chicago 10, Illinois.*

DISCUSSION

The basic procedures described have been used in the radiochemical laboratory of the Health Physics Branch of these laboratories for several months. The methods employed standard semimicroanalytical techniques. Precipitations were carried out in 50-ml. centrifuge tubes. Filtering and ignition were not required. Junior technicians achieved 50–75% yields based on added carrier.

Modifications were introduced as required. For example, it was sometimes necessary to remove silica from the insoluble portion of the melt by fuming with hydrofluoric and perchloric acids in platinum crucibles. This system was used if an analysis for ruthenium was not required. The sample was fumed with the acids, cooled, and cesium precipitated by addition of alcohol. The precipitate was dissolved in water, made alkaline with 0.5 *N* lithium hydroxide, and scavenged with 1 mg. of iron. The solution was adsorbed and eluted from an 8×30 mm. column of Duolite C-3, using reagents in the same ratio to column volume as above. The strontium and cerium were separated, purified, and precipitated as described.

For samples with a high concentration of anions (e.g. phosphate in fish specimens) it was advantageous to absorb the cations from 0.1 *N* acid solution on a Dowex 50 cation-exchange resin, wash the anions through with water, and elute the cations with 6 *N* hydrochloric acid. If an analysis of an anionic component such as P^{32} or S^{35} was required, this was a convenient method of preliminary separation.

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The author would like to thank Dr. Margaret Tutt, who did preliminary work on the methods, Dr. W. G. Cross, who designed and constructed the counter, and Mr. A. J. W. Hitchman for helpful discussion of the cesium method.

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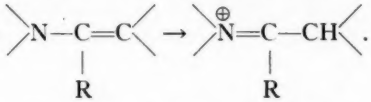
SUR LA TRANSFORMATION DE LA DIHYDROHÉTÉROCONESSINE EN DIHYDROCONESSINE[1]

H. FAVRE ET B. MARINIER[2]

SOMMAIRE

On montre que le diperchlorate de la base résultant de la déshydrogénation de la dihydro*hétéro*conessine par l'acétate mercurique est identique à celui que l'on obtient, par ce procédé, à partir de la dihydroconessine; ce diperchlorate est réduit catalytiquement en dihydroconessine. On en conclut que la dihydro*hétéro*conessine et la dihydroconessine sont bien des épimères en position 20; la configuration du groupe méthyle dans cette position peut être déterminée par ce procédé de déshydrogénation–réhydrogénation.

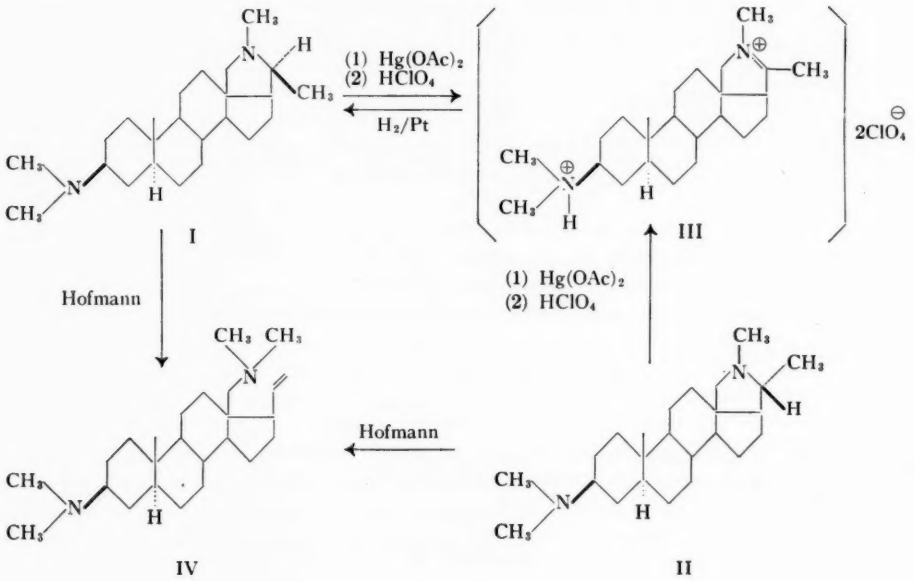
La constitution de la conessine, telle que proposée par Haworth, McKenna et leurs collaborateurs (1, 2), a été confirmée par des travaux récents (3, 4, 5). Un pas décisif dans les travaux de Haworth fut l'étude du système conessine–*hétéro*conessine qui conduisit à formuler ces deux isomères comme des epimères en position 20 (2, 6).

Nous rapportons dans ce mémoire la déshydrogénation par l'acétate mercurique de la dihydroconessine (I) et de la dihydro*hétéro*conessine (II). Bien que chacune de ces bases possède un groupe méthyl-imino et un groupe diméthyl-amino capables de réagir avec l'acétate mercurique (voir (7) pour de nombreuses références bibliographiques) un seul de ces groupes semble être le siège de la réaction. En effet, lorsque 1 mole des bases I ou II est traitée par 4 moles de réactif dans les conditions opératoires habituelles (7), deux atomes d'hydrogène seulement sont éliminés (cette détermination se fait en mesurant la quantité d'acétate mercureux qui précipite). On obtient dans les deux cas une base extrêmement altérable, qui forme toutefois un diperchlorate bien cristallisé et stable. La base déshydrogénée peut être isolée sous forme solide, p.f. 100–125°; tous nos essais de purification par cristallisation n'ont conduit qu'à des huiles jaunes; nous avons cependant réussi à en obtenir un spectre infrarouge acceptable: on y décèle une bande à 1645 cm.$^{-1}$. Les diperchlorates insaturés (en provenance de I et de II) sont identiques, comme le prouvent leur pouvoir rotatoire, leur point de fusion et leur spectre infrarouge qui présente en particulier une bande à 1690 cm.$^{-1}$. Le déplacement de la bande infrarouge de 1645 à 1690 cm.$^{-1}$ par formation du diperchlorate de la base déshydrogénée est caractéristique du système  , quand l'amine est tertiaire (7). A la réduction catalytique (platine) le diperchlorate III (issu soit de I, soit de II) absorbe une molécule d'hydrogène et conduit spécifiquement à la dihydroconessine.

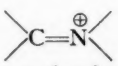
On sait, avec Haworth (2), que les bases isomères dihydroconessine (I) et dihydro*hétéro*conessine (II) se différencient uniquement par leur anneau hétérocyclique[3] et que l'ouverture de cet anneau, par dégradation selon Hofmann, supprime cette différence, comme le montre la formation de la dihydro-5,6 conessiméthine (IV) à partir de I et de II. On sait d'autre part que les bases *apo* et méthines—dont l'anneau hétérocyclique est ouvert—ont toutes une double liaison en 20–21,[4] à l'image de la base IV: ceci établit

[1]*Manuscrit reçu le 31 octobre, 1957.*
Contribution du Département de Chimie de l'Université de Montréal, Montréal, Qué.
[2]*Boursier du Conseil National de Recherches du Canada.*
[3]*Voir le travail (2) pour une discussion détaillée de ce point.*
[4]*On l'a amplement démontré (8, 9) en établissant des relations de synthèse et de dégradation entre l'apoconessine (diméthylamino-18 pregnatriène-3,5,20), la conessiméthine (bis-(diméthylamino)-3β,18 pregnadiène-5,20) et l'hydroxy-3β pregnadiène-5,20.*

indiscutablement que le carbone 17 n'est pas touché par le processus de formation de la double liaison en 20–21 et exclut l'hypothèse qui ferait de la conessine et de l'*hétéro*-conessine (par conséquent des bases I et II) des épimères en position 17. On peut donc considérer comme acquis que les bases I et II ne se distinguent ni par la position ou la configuration de leur groupe diméthylamino, ni par la configuration de leurs carbones 5 et 17.



I III IV II

La présence d'un groupement  dans le diperchlorate obtenu par déshydrogénation, la disparition chez ce dernier de la différence qui existe entre les bases saturées I et II et la transformation de la dihydro*hétéro*conessine en dihydroconessine ne peuvent se concevoir qu'en situant la double liaison dans l'anneau hétérocyclique et en fonction des formules I et II pour les bases saturées et de la formule III pour le diperchlorate de la base déshydrogénée. Si la déshydrogénation ne s'était pas portée sur le noyau hétérocyclique nous aurions obtenu à partir de I et de II deux produits de déshydrogénation distincts, reflétant encore la différence qui existait à l'origine entre I et II. La dihydroconessine et la dihydro*hétéro*conessine, et par suite la conessine et l'*hétéro*conessine, sont donc bien des épimères en position 20.

La grande instabilité de la base déshydrogénée, correspondant au diperchlorate III, ne nous a pas permis d'approfondir pour le moment les relations qui doivent exister entre sa liaison éthylénique et celle qui est localisée en position 17–20 chez les alcaloïdes du type de la conkurchine (10, 11). Le fait que la double liaison de la base de déshydrogénation puisse se placer en position 17–20, détruisant ainsi deux centres d'asymétrie dans l'anneau hétérocyclique, n'infirme pas la conclusion que nous tirons au sujet des structures épimères en position 20 des bases I et II, puisque ces dernières ne sont pas des épimères en position 17.

Le procédé de réduction mis en oeuvre pour passer de III à I amène en règle générale la fixation de l'hydrogène sur le côté le moins empêché de la molécule (12, 13); il est raisonnable ainsi d'admettre que le groupe méthyle se trouvera au-dessus du plan de l'anneau hétérocyclique dans le produit d'hydrogénation de III—donc dans la dihydroconessine (formule I). On rejoint de cette manière les conclusions de Černý, Lábler, et Šorm (3) et de Phillips et Johnson (4) relatives à la configuration du groupe méthyle en position 20 de la conessine.

Il convient cependant de signaler quelques différences dans le mode d'action de l'acétate mercurique sur I et sur II.

Le diperchlorate III, venant de la dihydroconessine (I), se présenta d'abord sous la forme de paillettes, p.f. 317°, puis sous la forme d'une poudre, p.f. 335–337°, lorsqu'on le cristallisa. Les spectres infrarouges de ces deux variétés sont très semblables. Cette hétérogénéité montre que la déshydrogénation qui amène en majorité la formation d'une seule double liaison s'accompagne de réactions secondaires. On peut théoriquement en retenir deux: (*a*) réaction du groupe diméthylamino en position 3; (*b*) hydroxylation sur le carbone 17, comme c'est le cas pour certaines bases tertiaires dont le carbone en β de l'azote est tertiaire, par exemple la méthyl-1 décahydroquinoléine (14); cette hydroxylation pourrait justifier la présence d'une bande —OH dans le spectre infrarouge de III. Ces réactions secondaires, quelles qu'elles soient, n'ont pu être décelées avec certitude en raison de la petite quantité de base mise en oeuvre dans nos expériences.

La déshydrogénation de la dihydro*hétéro*conessine n'engendra que le diperchlorate à point de fusion élevé; le rendement en sel brut fut de 64% seulement, comparé à 85% dans le cas de la dihydroconessine. Il est raisonnable d'attribuer ces différences à l'accessibilité plus ou moins grande de l'hydrogène en position 20 chez I et II.

PARTIE EXPÉRIMENTALE[5]

Déshydrogénation de la dihydroconessine

A 1.424 g. (0.00446 mole) d'acétate mercurique dans 12 ml. d'acide acétique aqueux à 5%, on ajoute 0.400 g. (0.00114 mole) de dihydroconessine, p.f. 109°, $[\alpha]_D^{22} = +50.4°$ ($c = 3.0$; $CHCl_3$ (2, 15)). Le mélange agité mécaniquement est chauffé au bain-marie durant 1½ heure. L'acétate mercureux apparaît après 2 à 3 minutes de chauffage. On l'élimine par essorage: 0.512 g. (soit 88.5% de ce qui est nécessaire pour éliminer deux atomes d'hydrogène); on peut déceler dans ce précipité une petite quantité de mercure. Le filtrat est saturé avec H_2S; le précipité noir est séparé du liquide par centrifugation. La solution brunâtre est recueillie, refroidie à 0° et rendue alcaline avec NaOH 50% (2–3 ml.); un solide précipite; on ajoute de l'eau et on extrait trois fois par de l'éther. Les solutions éthérées réunies sont lavées à l'eau, séchées sur du sulfate de sodium anhydre et traitées à 0° par 0.5 ml. (jusqu'au virage bleu du Congo) d'une solution faite de volumes égaux d'acide perchlorique 70% et d'éthanol 95%. Le diperchlorate précipite et après quelques heures on le recueille par essorage: 0.527 g. (85% de la théorie), poudre blanche, p.f. 307–310° (bloc Maquenne). Après une cristallisation dans l'éthanol 95% on obtient des paillettes jaune pâle, p.f. 317° (bloc), dont le spectre infrarouge: bande forte 1694 cm.$^{-1}$, $\diagup\!\!\overset{\oplus}{\mathrm{N}}\!\!=\!\mathrm{C}\diagdown$, bande moyenne 3060 cm.$^{-1}$, $-\overset{|}{\underset{\oplus}{\mathrm{N}}}\mathrm{H}-$, et

[5]*Les points de fusion (p.f.) ne sont pas corrigés; sauf indication contraire ils ont été déterminés dans un appareil de Thiele. Les spectres infrarouges ont été déterminés à l'aide d'un spectromètre "Perkin-Elmer", modèle 112, à simple faisceau et parcours double, optique* NaCl.

bande très faible 3620 cm.$^{-1}$ (présence de —OH). Une cristallisation de ces feuillets dans l'éthanol 95% donne une poudre jaune pâle, p.f. 335–337° (bloc), $[\alpha]_D^{24} = +29.9°$ ($c = 1.0$; tétrahydrofuranne–eau: 8–2). Spectre infrarouge (nujol): bande forte 1690 cm.$^{-1}$, $\rangle\overset{\oplus}{N}{=}C\langle$, bande moyenne 3110 cm.$^{-1}$, $-\underset{\oplus}{\overset{|}{N}}H-$, et bande très faible 3620 cm.$^{-1}$ (présence de —OH). Calculé pour $C_{24}H_{40}N_2.2HClO_4$: C, 51.70; H, 7.59; N, 5.02%. Trouvé[6]: C, 51.76; H, 7.60; N, 4.95%. Le rendement en diperchlorate cristallisé est de 0.303 g. (49%).

A 0.007 g. de diperchlorate en suspension dans 1 ml. d'eau on ajoute 1 ml. de NaOH 50% et 10 ml. d'eau; on extrait trois fois avec de l'éther. Après les lavages habituels, on évapore l'éther sous vide partiel; on obtient 0.004 g. d'un solide jaune très pâle, p.f. 100–125°. Cette amine est très instable et jaunit rapidement à l'air. Spectre infrarouge (nujol): bande forte à 1645 cm.$^{-1}$, $\rangle C{=}C\langle$.

Déshydrogénation de la dihydrohétéroconessine

La dihydro*hétéro*conessine (0.404 g.), p.f. 105°, $[\alpha]_D^{22} = +17°$ ($c = 1.8$; $CHCl_3$ (2, 15)), est déshydrogénée dans les conditions décrites plus haut. L'acétate mercureux commence à précipiter au bout de 5 minutes de chauffage. Il ne contient pas de mercure lorsqu'on le recueille à la fin de la réaction: 0.546 g. (94.1% de ce qui est nécessaire pour éliminer deux atomes d'hydrogène). On obtient 0.400 g. de diperchlorate brut (64.2%) sous forme de poudre blanche; après deux cristallisations dans l'éthanol 95% on a une poudre blanche: 0.187 g. (30%), p.f. 338° (bloc; ne donne pas de dépression de point de fusion avec le diperchlorate décrit plus haut, p.f. 335–337°); $[\alpha]_D^{24} = +29.7°$ ($c = 1.0$; tétrahydrofuranne–eau: 8–2). Spectre infrarouge (nujol): bande forte 1690 cm.$^{-1}$, $\rangle\overset{\oplus}{N}{=}C\langle$, bande moyenne 3110 cm.$^{-1}$, $-\underset{\oplus}{\overset{|}{N}}H-$, et bande très faible 3640 cm.$^{-1}$ (présence de —OH).

Hydrogénation catalytique des diperchlorates

(*a*) *Diperchlorate en provenance de la dihydroconessine.*—Le diperchlorate (0.100 g.) dans 2.5 ml. d'un mélange dioxanne–eau: 8–2, est hydrogéné en présence de 15 mg. de platine hydrogéné au préalable. L'absorption d'hydrogène cesse au bout d'une heure: absorbé, 4.76 ml.; calculé pour 1 H_2, 4.48 ml., pour 756 mm. et 25°. On essore le catalyseur, dilue le filtrat avec de l'eau, rend alcalin avec NaOH 50% et extrait avec de l'éther. On isole à la manière habituelle 0.062 g. (97%) de solide jaune pâle, p.f. 103°. Ce composé brut ne donne pas de dépression de p.f. en mélange avec de la dihydroconessine, mais le mélange avec la dihydro*hétéro*conessine accuse une dépression et fond à 85° environ. Après une cristallisation dans l'acétone, on retire 0.038 g. de cristaux, p.f. 106.5°, $[\alpha]_D^{25} = +49.4°$ ($c = 3$; $CHCl_3$) et 0.010 g. de cristaux, p.f. 103.5°. Le rendement total en dihydroconessine est de 0.048 g. ou 75%.

(*b*) *Diperchlorate en provenance de la dihydrohétéroconessine.*—Ce diperchlorate (0.100 g.) absorbe la quantité théorique d'hydrogène en 55 minutes dans des conditions opératoires semblables à celles décrites sous (*a*). On obtient 0.064 g. (100%) de dihydroconessine brute, p.f. 103°, et après cristallisation dans l'acétone 0.036 g., p.f. 106.5°, $[\alpha]_D^{25} = +50°$ ($c = 3$; $CHCl_3$) et 0.018 g., p.f. 104°, soit 0.054 g. ou 84.4%. Les p.f. de mélange ont été déterminés avec la dihydroconessine (aucun abaissement) et avec la dihydro*hétéro*conessine (abaissement à 89°).

[6]*L'analyse fut effectuée par M. W. Manser, Herrliberg.*

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THE CHEMISTRY OF PEAT

PART I. THE STEROLS OF PEAT MOSS (SPHAGNUM)[1]

D. A. J. IVES[2] AND A. N. O'NEILL

ABSTRACT

Peat moss (*Sphagnum*) from the surface of an Atlantic peat bog has been extracted with a mixture of benzene and ethanol. The extract has been fractionated chromatographically on alumina. A mixture of sterols has been isolated from one fraction. This mixture has been proved by oxidation experiments to consist of β-sitostanol (stigmastanol) and β-sitosterol. It constituted approximately 0.2% by weight of the dried peat moss.

INTRODUCTION

A considerable amount of work has been done on the chemical composition of peat (8), lignite (brown coal) (8), and coal (8), but relatively little on the composition of peat moss (*Sphagnum*). The latter is considered to be the main precursor of peat in the Atlantic area of Canada. This work was undertaken in an effort to remedy this defect, and also to ascertain what chemical changes occur in humification. Black and his co-workers (4) carried out an extensive analysis on a sample of peat moss from Scotland and reported the presence of β-sitosterol.

The peat moss used in our experiments was a living surface moss, from Shipigan, New Brunswick, and was essentially a mixture of *Sphagnum fuscum*, *S. capillaceum*, and *S. magellanicum* with the first two predominating. It was comparatively free of other common bog plants. The moss was dried to a moisture content of approximately 5% and ground to pass through a 20-mesh screen. Only relatively small quantities of the powder could be extracted at a time, owing to its bulk. The process used was a continuous extraction method, with a constant stream of pure solvent passing through the moss.

After evaporation of the solvent, the dark brown gum (approximately 6% of the total solids) was saponified with methanolic potassium hydroxide solution and the unsaponifiable material extracted with ether. This extract (approximately 1.5% of the total solids), after evaporation, was dissolved in light petroleum and chromatographed roughly on alumina. A small portion of the gum (approximately 3%) did not dissolve in the petrol and was kept for further investigation. The eluate from the chromatogram was divided into five fractions: materials eluted progressively by (*a*) light petroleum, (*b*) benzene, (*c*) ether, (*d*) ether containing 10% methanol, and (*e*) methanol. These fractions will be described separately. The composition of fractions (*c*) and (*d*) varied from extraction to extraction and with the grade of alumina used. The ether fraction sometimes consisted of a white, low-melting solid, and the ether–methanol fraction of a colorless crystalline solid, subsequently proved to be the sterols. In the majority of extractions, however, the components were mixed and tended to be removed from the column together in fraction (*d*) as a light yellow glass. The mixture was separated into cyclic and linear aliphatic compounds by treatment with urea with which the latter formed an insoluble complex. Decomposition of the complex yielded an alcohol which has been tentatively identified as lignoceryl alcohol by melting point, mixed melting point, and molecular weight.

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The colorless crystalline material, which did not form a complex with urea, when obtained relatively pure gave a strong Liebermann–Burchard test, which indicated that it was a sterol or triterpene. The melting point was 135°–137°, but the optical rotation tended to vary from −12° to −24°. The latter depended on which fraction was taken in the chromatogram. The average value obtained was −18°. These constants were unchanged by many recrystallizations or by careful chromatographic separation into about 200 fractions. From this it was at first assumed that two sterols were present with rotations of −12° and −24°, but the infrared spectra of the two materials were identical and only differed slightly in the intensities of certain peaks. Subsequent work showed that the sterols were actually an inseparable mixture of β-sitostanol (stigmastanol) and β-sitosterol in various proportions. The infrared spectrum of the mixture indicated the presence of a secondary hydroxyl group from bands at 3584 and 1050 cm.$^{-1}$ and the presence of only one double bond from bands at 837 and 800 cm.$^{-1}$. This bond was of the type >C=CH—, and the spectrum bore a striking resemblance to that of the 5,6-double bond in cholesterol, which has bands at 839 and 800 cm.$^{-1}$. In confirmation of this the infrared spectrum of fucosterol, which has a 24,28-double bond besides the nuclear one, was markedly different from those of cholesterol and the sterols from peat moss. From this it was inferred that there was no double bond in the side chain of the sterols under investigation.

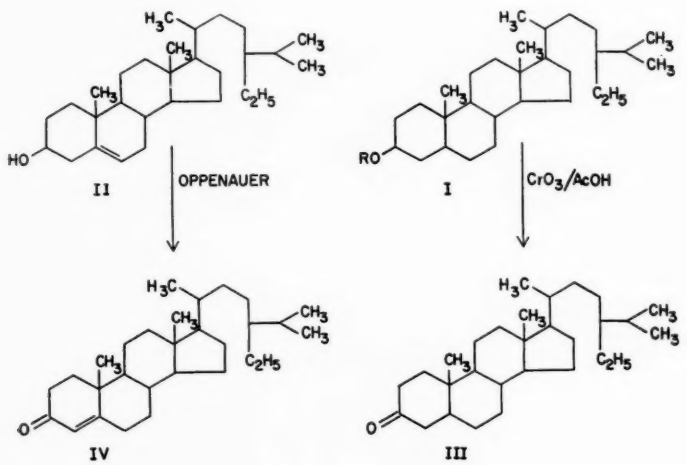
On catalytic hydrogenation the mixture gave pure β-sitostanol, identified by its melting point and rotation, and the melting points and rotations of the derived acetate and ketone. This indicated that the components of the mixture differed only in the degree or position of unsaturation. As already stated the infrared spectrum indicated a nuclear double bond and preliminary oxidation showed that this double bond was in a position to give an α,β-unsaturated ketone. There remained the possibility that some of the material had the double bond in the nucleus in a position other than the 5,6. The only remaining positions for a secondary–tertiary double bond in a six-membered ring are the 7,8-position and the 9,11-position. On attempted hydrogenation with platinum as a catalyst and in the presence of acetic acid, the 7,8-double bond will migrate to the 8,14-position (3), which is stable to hydrogenation, and requires treatment with hydrochloric acid before moving to the 14,15-position where it can be reduced (10). To date no natural sterol has been found with a 9,11-double bond. It is probable that under slightly acid conditions this bond would migrate to the 8,9-position, and attempted hydrogenation of sterols with this type of double bond will rearrange the double bond to the 8,14-position again (12, 13). Since the reduced material obtained from the hydrogenation was completely saturated, it seemed logical to assume from the above evidence that we were dealing with a mixture of β-sitostanol and β-sitosterol. This assumption has been proved correct by chemical evidence.

A further attempt to separate the mixture by chemical means failed. This involved treating the mixture with bromine and trying to recover the less soluble β-sitosterol dibromide by recrystallization. No pure crystalline dibromide was obtained however.

The composition was finally established by oxidation. The sterol mixture was oxidized with chromium trioxide in acetic acid solution. Under these conditions β-sitostanol (I) will be readily oxidized to β-sitostanone (III). β-Sitosterol, on the other hand, will form a variety of products arising from oxidation of the double bond (6). All these products will have two or more oxygen atoms, and will thus be more polar in character than β-sitostanone. In agreement, chromatography of the oxidation product first gave β-sitostanone (III), proved by melting point, rotation, and mixed melting point with an authentic specimen, followed by a series of non-crystalline oils.

Oxidation of the sterol mixture to give β-sitostenone (IV) alone was achieved by the Oppenauer method with aluminum isopropoxide. The yield, however, was poor and some oxidation of the β-sitostanol took place (7). To parallel the above work, the mixture of sterols was oxidized in such a manner as to give both β-sitostenone and β-sitostanone. This was achieved by brominating the mixture, oxidizing the β-sitosterol dibromide and β-sitostanol in a two-phase system with chromium trioxide (9), removing the bromine from the dibromide by means of sodium iodide (11), and chromatographing the resulting mixture. Both β-sitostenone and β-sitostanone were obtained, although the former was not quite as pure as desirable. From the infrared spectrum the contaminant appeared to be β-sitostanone, and the two ketones are known to be fairly difficult to separate by chromatography (7).

The proportions of β-sitostanol and β-sitosterol present in the steroid mixture obtained can be calculated directly from the rotations of the pure sterols and the rotation of the mixture. From these figures the percentage of β-sitostanol varied from 20% to 40%, with an average value of 30%. The oxidation experiments carried out to determine the chemical composition were not accurate enough to give physical composition since the yields varied and were never 100%.



EXPERIMENTAL

All rotations were measured in a 1-dm. tube with a Rudolph polarimeter. Melting points were observed on a Kofler micro melting point apparatus and are corrected. The ultraviolet spectra were determined in ethanolic solution with a Beckman Model DU spectrophotometer. The infrared spectra were determined in carbon disulphide solution with a Baird double-beam infrared spectrophotometer model 4-55. Light petroleum refers to the fraction with boiling point 35°–60°.

Extraction of Peat Moss

The dried and ground peat moss (2.5 kg.) was loaded into a large copper percolator equipped with a pump and overflow system which permitted fresh solvent to percolate continuously through the bed. This was essentially a countercurrent extraction system. The solvent used was a mixture of benzene and ethanol (3:2, 40 liters). It was run slowly through the moss, at a rate which was controlled by a valve at the bottom of the extraction

apparatus. The extraction usually required about 12 hours. The resulting extract was concentrated to 2 liters at 50° under reduced pressure in a climbing film evaporator. Potassium hydroxide (100 g.) in methanol (500 ml.) was then added and the mixture heated under reflux for 2 hours. The mixture was diluted with water and extracted with ether, the ether extract washed and evaporated to dryness, to give the crude unsaponifiable extract. The acids were obtained by acidification of the alkali-soluble fraction followed by filtration.

Treatment of Crude Extract

The crude extract (35 g.) was dissolved in light petroleum (500 ml.). A small portion of the material which did not dissolve was removed by centrifugation for later investigation. The main bulk of the petrol solution was added to the top of a column (55×5 cm.) of alumina. The column was eluted with light petroleum (2 liters), benzene (2 liters), ether (6 liters), ether–methanol (9:1, 3 liters), and methanol (1.5 liters). The amounts of material eluted were approximately as follows: from the petrol fraction, 1 g.; benzene, 1.5 g.; ether, variable (see text, max. of 4.5 g.); ether–methanol, variable (see text, max. of 10 g.); methanol, 6–7 g.

Separation of Sterols from Crude Combined Fractions

The partly crystalline mixture (10 g.) obtained by solvent removal from the ether–methanol eluate was dissolved in light petroleum (500 ml.) and added to a mixture of urea (15 g.) made slushy with methanol. The mixture was shaken for 1 hour, and the resulting urea complex filtered off. The filtrate was again treated with a second batch of urea, but very little more material was precipitated. The petrol solution was evaporated to 250 ml., refiltered, and washed twice with distilled water to remove any remaining complex. The solution was evaporated to dryness and the product crystallized from aqueous ethanol to give a white crystalline material (4.5 g.), m.p. 135°–137°, $[\alpha]_D^{26}$ −18° (c = 1.4 in chloroform). The material complexed by the urea was recovered by treating the complex with hot water for 1 hour and extracting with benzene, washing the extract well and evaporating to dryness to give a white, waxy solid (5 g.). This was recrystallized from carbon tetrachloride, m.p. 75.5°–76.5°. It was optically inactive and a mixed melting point with lignoceryl alcohol of m.p. 74° was undepressed. Anal. Calc. for $C_{24}H_{50}O$: C, 81.27; H, 14.21; mol. wt. 354. Found: C, 81.64; H, 14.01; mol. wt. 372 (ebullioscopic in butanone), 347 (Rast). Bleyberg and Ulrich (5) report a melting point of 75.4° for lignoceryl alcohol. The alcohol was oxidized with chromic acid in acetic acid and benzene to yield an acid of melting point 81°–82°. This value is in good agreement with values reported for lignoceric acid.

Reduction of Sterols

A portion (500 mg.) of the sterol mixture obtained from the above separation was dissolved in ethyl acetate (100 ml.) and acetic acid (5 ml.). Platinum oxide (50 mg.) was added and the mixture shaken with hydrogen at a pressure of 40 p.s.i. overnight. The platinum was then filtered off and the filtrate washed free of acetic acid and evaporated to dryness. The resulting product was crystallized from aqueous ethanol to give β-sitostanol, m.p. 140°–141° (melts and resolidifies at 136°), $[\alpha]_D^{25}$ +24° (c = 1.2 in chloroform). The values recorded in the literature are m.p. 141°–142°, $[\alpha]_D$ +24° (1).

Acetylation

β-Sitostanol (100 mg.) was dissolved in pyridine (2 ml.) and acetic anhydride (3 ml.) added, and the mixture heated on the steam bath for 1 hour. The mixture was diluted with benzene, washed with dilute alkali, dilute acid, and water, and evaporated to

dryness. The product was crystallized from chloroform–methanol to give β-sitostanol acetate, m.p. 135°–136°, $[\alpha]_D^{26}$ +15° (c = 1.0 in chloroform). The values recorded in the literature are m.p. 138°–139°, $[\alpha]_D$ +15° (1).

Oxidation

β-Sitostanol (100 mg.) was dissolved in acetic acid (10 ml.), and chromium trioxide (20 mg.) in water (1 ml.) and acetic acid (10 ml.) added. The solution was allowed to stand overnight at room temperature, then diluted with water and extracted with benzene. The benzene extract was washed free of acetic acid and evaporated to dryness. The resulting crude product was dissolved in benzene and filtered through alumina. Evaporation of the solvent yielded a material which was crystallized from chloroform–methanol to give β-sitostanone, m.p. 155°–157°, $[\alpha]_D^{26}$ = +38° (c = 1.28 in chloroform). The 2,4-dinitrophenylhydrazone made in the usual manner was yellow and had m.p. 221° (dec.). For this compound Barton (2) reports m.p. 157°, $[\alpha]_D$ +38°, and the m.p. of the yellow 2,4-dinitrophenylhydrazone 223° (dec.).

Oxidation of Sterols

The sterol mixture (1 g.) was dissolved in acetic acid (15 ml.), and chromium trioxide (60 mg.) in water (1 ml.) and acetic acid (10 ml.) added. The mixture was allowed to stand at room temperature for 1 hour, then diluted with water and extracted with benzene. The benzene extract was washed well and evaporated to dryness. The crude material was chromatographed on alumina and eluted with benzene to afford β-sitostanone (50 mg.), m.p. 156°–157°, undepressed in mixed m.p. with a genuine specimen, $[\alpha]_D^{24}$ +37° (c = 1.3 in chloroform).

Oxidation of Sterols

The sterol mixture (1 g.) was dissolved in dry acetone (15 ml.), and aluminum isopropoxide (1 g.) in dry benzene (30 ml.) added. The solution was heated under reflux overnight, then diluted with water, washed twice with 2 N sulphuric acid and water, and the benzene layer evaporated to dryness. The crude oil obtained was heated on the steam bath under reduced pressure for 1 hour, then chromatographed carefully. Elution with petrol–benzene (2:1) gave a small amount of β-sitostanone (30 mg.), identified by m.p. and mixed m.p. Elution with benzene–petrol (3:1) gave β-sitostenone (120 mg.), m.p. 87°–88°, λ_{max} = 241, ϵ_{max} = 17,000. Barton and Jones (2) give m.p. 88°, λ_{max} = 240.5, ϵ_{max} = 20,000.

Oxidation of Sterols

The sterol mixture (4 g.) was dissolved in chloroform (30 ml.) and acetic acid (30 ml.). Sodium acetate (400 mg.) in acetic acid (10 ml.) was added and the solution cooled to 0°. A solution of bromine (1.5 g.) in acetic acid (10 ml.) also cooled to 0° was then added. The resulting solution was then washed with sodium thiosulphate solution to remove the excess bromine and then with water, and then evaporated to dryness. The crude material so obtained was dissolved in benzene (50 ml.) and shaken with a solution of chromium trioxide (1.5 g.) in water (15 ml.) and acetic acid (25 ml.) for 6 hours. The benzene solution was washed thoroughly to remove acetic acid and evaporated to dryness. The crude yellow oil obtained was dissolved in acetone, and sodium iodide (7 g.) in acetone (30 ml.) added. The mixture was heated under reflux for 3 hours, diluted with benzene, and washed with sodium thiosulphate solution and water, and evaporated to dryness. Chromatography of the crude oxidation product on alumina and elution with benzene gave β-sitostanone (200 mg.), identified by m.p. and mixed m.p. Elution with

benzene–ether (19:1) gave β-sitostenone (1.25 g.), m.p. 86°–87°, $[\alpha]_D^{25}$ +78° (c = 1.13 in chloroform), λ_{max} = 241, ϵ_{max} = 16,000. The value recorded in the literature for the rotation is $[\alpha]_D$ +85° (11).

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ORGANIC DEUTERIUM COMPOUNDS

XIX. SYNTHESIS OF SOME DEUTERATED LAURIC ACIDS AND THEIR METHYL ESTERS[1]

M. ELAINE ISABELLE AND L. C. LEITCH

ABSTRACT

The synthesis of lauric acids deuterated in the carboxyl, the terminal methyl, and the α-methylene groups and in various combinations of these is described. The methyl and methyl-d_3 esters of each of the acids were also prepared.

Two further examples of homolytic halide addition to olefins are reported.

The reaction between alkyl halides and silver acetylides is described. A mechanism involving a new type of free radical is postulated.

In connection with studies by Jones and co-workers (9) on the infrared spectra of aliphatic fatty acids and their methyl esters it became necessary to prepare a number of deuterated lauric acids and methyl laurates. The series of compounds synthesized in this work are shown below.

$CH_3(CH_2)_{10}CO_2R$ (I) $\qquad$ $CH_3(CH_2)_9CD_2CO_2R$ (III)

$CD_3(CH_2)_{10}CO_2R$ $\qquad$ $CD_3(CH_2)_9CD_2CO_2R$

(R = H, D, CH_3, CD_3)

The compounds in the first group presented no particular problem. Lauric acid-*d* was obtained by decomposing lauroyl chloride with deuterium oxide. Methyl-d_3 laurate was obtained in excellent yield by heating silver laurate with methyl-d_3 bromide (14).

The synthesis of the key compound in the second series, lauric acid labelled on the terminal carbon atom of the chain, proved more difficult. Since methyl-d_3 iodide of high isotopic purity is now readily available, the preparation of the deuterolauric acid in question was attempted by the reactions shown below:

$$CD_3I + NaC{\equiv}C(CH_2)_8CO_2CH_3 \rightarrow CD_3C{\equiv}C(CH_2)_8CO_2CH_3 + NaI,$$

$$CD_3C{\equiv}C(CH_2)_8CO_2CH_3 \rightarrow CD_3(CH_2)_{10}CO_2CH_3.$$

In pilot experiments with methyl iodide, however, we were unable to methylate the sodium derivative of methyl 10-undecynoate in liquid ammonia. This observation is in agreement with that of Taylor and Strong (20), who found that the alkynes $CH_3(CH_2)_mC{\equiv}CH$ did not condense in sodamide – liquid ammonia with $I(CH_2)_nCl$ where $m < 10$ or $n < 3$. Attempts to alkylate by this method were therefore abandoned.

The reaction of deuterated alkyl iodides (and even bromides) with the silver salts of aliphatic acids is a very convenient reaction for the synthesis of deuterated esters (13) and was used above to prepare methyl-d_3 laurate. There was a possibility that silver acetylides would also react under suitable conditions, at least with methyl iodide, to give alkylacetylenes. Observations in the literature (6) relating to the inertness of silver acetylides to alkyl halides were ignored, and the silver derivative of methyl 10-undecynoate was heated to 75° C. for several hours with an excess of methyl iodide. It was an agreeable surprise to isolate methyl 10-dodecynoate although in only 40 to 50% yields. The new ester was identified by its infrared spectrum, which showed no absorption

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for acetylenic hydrogen, and by the melting point of the acid; it was evidently methyl 10-dodecynoate. A similar reaction was found to take place with ethyl iodide to give methyl 10-tridecynoate. It therefore appears that silver acetylides will react with certain alkyl halides. The synthesis is particularly valuable with labelled halides owing to the ease with which unreacted halide may be recovered.*

In order to avoid using a large excess of labelled methyl iodide an experiment was next carried out in ether as a solvent. The product isolated from the reaction was not pure methyl 10-dodecynoate; its index of refraction was low, the melting point of the 10-dodecynoic acid was also low, and the ester gave a precipitate of the silver acetylide when shaken with ammoniacal silver nitrate in alcohol. The product seemed to be a mixture of methyl 10-undecynoate and 10-dodecynoate.

Several other runs were made in ether or benzene as solvent and in one case, in the absence of methyl iodide. The results of these experiments, which show the yield of ester, its index of refraction, and the melting point of the acid obtained on hydrolysis, are given in Table I.

TABLE I

INFLUENCE OF SOLVENT ON THE YIELD AND PURITY OF THE METHYL 10-DODECYNOATE

Wt. of silver derivative (g.)	Vol. of methyl iodide (ml.)	Solvent (ml.)	Yield (ml.)	n_D^{20}	M.p. of acid (°C.)
12.7	10.0	None	4.0	1.4529	51
13.7	10.0	10 ml. ether	5.4	1.4510	47
10.0	4.0	10 ml. ether	0.5	1.4500	–
6.0	5.0	10 ml. C_6H_6	1.0	1.4480	–
6.0	5.0	None	–	1.4516	50–51
6.0	None	10 ml. ether	1.0	1.4460	42–43

The formation of methyl 10-undecynoate in the presence of ether may well take place by a free radical mechanism. According to this view the silver acetylide would produce the radical $CH_3OOC(CH_2)_8C{\equiv}\dot{C}$ mentioned in reference 11, which could then give rise to the acetylenic ester by abstraction of a hydrogen atom from the solvent or from the ester itself:

$$CH_3OOC(CH_2)_8C{\equiv}CAg \rightarrow CH_3OOC(CH_2)_8C{\equiv}\dot{C} + Ag,$$

$$CH_3OOC(CH_2)_8C{\equiv}\dot{C} + C_2H_5OC_2H_5 \rightarrow CH_3OOC(CH_2)_8C{\equiv}CH + \dot{C}_2H_4OC_2H_5.$$

The following observations are submitted as evidence in favor of this mechanism. When the silver derivative of methyl 10-undecynoate was heated alone in a sealed tube, a silver mirror was formed and a small yield of methyl 10-undecynoate was obtained. Much polymeric material was found. Moreover, when the acetylide was heated in benzene-d_6, a product was isolated which had a small band in the region of the acetylenic deuterium vibration. Waters (23) is inclined to believe that silver derivatives ought to participate readily in free radical reactions because of the weak electropositive character of silver. Also, Glockling (5) has shown that the heterogeneous decomposition of iso-1-butenyl silver gives rise to iso-1-butenyl radicals, $(CH_3)_2C{=}\dot{C}H$. On the basis of all this evidence we submit that a $CH_3OOC(CH_2)_8C{\equiv}\dot{C}$ radical is involved in the present reactions and that the formation of methyl 10-undecynoate in the presence of ether takes place by abstraction of hydrogen from the solvent or from the ester itself.

**After this work was completed Davis and Schreiber (3) reported the synthesis of acetylenic ketones by reaction of the silver derivatives of 1-hexyne and 1-octyne with acid chlorides in* CCl_4.

Regarding the alkylation of the silver acetylide by methyl and ethyl iodides, one is tempted to invoke a free radical mechanism and represent the reaction by the steps shown below:

$$CH_3OOC(CH_2)_8C{\equiv}CAg \rightarrow CH_3OOC(CH_2)_8C{\equiv}\dot{C} + Ag,$$

$$CH_3I + Ag \rightarrow \dot{C}H_3 + AgI,$$

$$CH_3 + CH_3OOC(CH_2)_8C{\equiv}\dot{C} \rightarrow CH_3OOC(CH_2)_8C{\equiv}CCH_3.$$

However, the formation of methane by abstraction of hydrogen from the solvent or of ethane by dimerization, which are normal reactions of free radicals, has not been observed in these experiments.

In view of the comparative stability of the ions $R.C{\equiv}C^-$, it is possible that the alkylation takes place by a "push-pull" mechanism via the transition state shown below:

$$R.C{\equiv}C^- + CH_3I \xrightarrow{Ag^+} R.C{\equiv}C\cdots CH_3\cdots I \rightarrow R.C{\equiv}CCH_3 + AgI.$$

With methyl-d_3 iodide, methyl 10-dodecynoate deuterated on the terminal carbon atom of the chain was obtained. Reduction in an alkaline medium by the method of Schwenk *et al.* (19) gave lauric-12-d_3 acid from which methyl laurate-12-d_3 was obtained on esterification. There was no evidence of α-deuteration as judged from the infrared spectra of the acid or ester.

Lauric-12-d_3 acid was also synthesized by an alternative method. Jensen, Kharasch, and Urry have reported the peroxide induced addition of polyhalogenomethanes to olefins (7). It has now been found that addition of chloroform to methyl undecylenate gives a mediocre yield of methyl 12-trichlorolaurate. Dechlorination of the ester by means of zinc and acetic acid-*d* gave an 80% yield of methyl laurate-12-d_3. Deuterium oxide – dioxane mixtures can also be employed for the dehalogenation, and thus the necessity of preparing acetic acid-*d* can be avoided. Infrared spectra gave no evidence of α-deuteration in the acid or ester. The other members of this series of deuterated lauric acids were prepared by methods already described for lauric acid itself (7).

The third series of compounds involved the preparation of lauric acid deuterated on the α-methylene group. Interest was focused first on α-dibromolauric acid as a starting material. Textbooks on organic chemistry often make the general statement that further bromination of an α-bromo acid chloride by the Hell-Volhard method leads to the α-dibromo acid chloride. However, there are few references to these acids or their derivatives in the literature to substantiate this statement. α,α-Dibromoheptanoic acid has been reported but it was prepared from *n*-heptaldehyde diacetal (2), not from the acid. α,α-Dibromobutyric acid was supposedly formed when α-bromobutyric acid was heated with excess bromine in a sealed tube (15). Bromination of lauric acid beyond the α''-bromo stage in sealed tubes was completely unsuccessful in our hands in that inseparable mixtures of polybromobutyric acids seemed to be formed.

The required methyl ester was synthesized by making use of another peroxide induced addition to olefins. Methyl dichloroacetate was found to add readily to 1-decene to give a mediocre yield of methyl 2,2-dichlorolaurate. Dechlorination with deuterium oxide in dioxane and zinc dust gave an excellent yield of methyl laurate-2,2-d_2 (III; R=CH_3). The other members of this series were obtained as already described for the normal acid.

The final series of deuterated lauric acids and their esters (IV) were prepared from methyl laurate-12-d_3 by the following route:

$$(CO_2C_2H_5)_2 + CD_3(CH_2)_{10}CO_2CH_3 \xrightarrow{C_2H_5OK} CD_3(CH_2)_9CH(CO_2CH_3)_2$$

$$CD_3(CH_2)_9CH(CO_2CH_3)_2 \xrightarrow{^-OD} CD_3(CH_2)_9CD(CO_2D)_2$$

$$CD_3(CH_2)_9CD(CO_2D)_2 \longrightarrow CD_3(CH_2)_9CD_2CO_2D + CO_2.$$

The reactions were first carried out with the normal ester. The Claisen condensation with methyl laurate to *n*-decyl malonic ester took place readily and the yields from there on were nearly quantitative (17, 18). Similar syntheses were then carried out with the terminally labelled ester; thus lauric acid labelled on both the α-methylene and the terminal carbon atom of the chain was obtained.

An interesting observation relative to the 1420 cm.$^{-1}$ band of fatty acids in the infrared came to light on comparison of the spectra of the acids in carbon tetrachloride solution. Jones (8) has attributed the 1420 cm.$^{-1}$ band to the scissoring vibrations of the α-methylene group in $R.CH_2CO_2CH_3$. When the spectrum of α-deuterated lauric acid was examined it still showed a band of medium intensity at 1417 cm.$^{-1}$. It seemed most unlikely that deuterium would have been lost by exchange in the α-position during hydrolysis of the ester. The band was also present but of reduced intensity in the acid after exchange with deuterium oxide. However, it was entirely absent from the spectrum of the α-deuterated acid chloride. It was likewise absent from the spectrum of methyl 2,2-dichlorolaurate and 2,2-dichlorolauroyl chloride. It was present, however, in the spectrum of lauroyl chloride and lauronitrile. The absorption in the 1420 cm.$^{-1}$ region is therefore not due solely to the α-methylene but also to the hydroxyl group. The spectrum of lauric acids labelled in the methyl group showed no absorption in the 1380 cm.$^{-1}$ region. Quantitative studies on the spectra of these acids by Jones and co-workers now in progress will be reported by them in detail elsewhere.

EXPERIMENTAL

Lauroyl Chloride

Lauric acid (1.0 g.) was warmed on the steam bath with 1 ml. of thionyl chloride (purified by distillation over quinoline and linseed oil). After 4 hours' heating, excess thionyl chloride and hydrogen chloride were pumped off. The residue was then twice distilled on the vacuum line in a Späth bulb. Yields: 0.8 ml., n_D^{20} 1.4455. Its infrared spectrum showed no absorption in the 3000–3600 cm.$^{-1}$ region and the band at 1407 cm.$^{-1}$ was reduced to one-half of its intensity in the spectrum of lauric acid where it appears at 1417 cm.$^{-1}$.

Lauric Acid-d

Lauroyl chloride was warmed on the steam bath for 1 hour with 2.0 ml. of deuterium oxide. After hydrolysis the lauric acid-*d* was extracted with pentane. After one recrystallization from pentane, 0.8 g. of acid was obtained. Since the acid still showed some absorption in the 3000–3400 cm.$^{-1}$ region in the infrared, it was exchanged by being heated with 10 ml. of deuterium oxide on the steam bath overnight. The equilibrated product was worked up as already described. There was little if any change in its spectrum by this treatment. The intensity of the band at 1417 cm.$^{-1}$ was the same as that in lauroyl chloride; part of it was masked by the absorption in the 1325–1410 cm.$^{-1}$ region. There was slight absorption in the 3000–3600 cm.$^{-1}$ region due to the presence of residual OH.

Methyl-d_3 Laurate, $CH_3(CH_2)_{10}CO_2CD_3$

Silver laurate was prepared as described in reference 12 by adding at the same rate

equivalent amounts of aqueous silver nitrate and potassium laurate to hot water, with stirring. The precipitate was filtered off, washed with water, and then acetone, and dried under vacuum in the dark.

Six grams of thoroughly dry silver laurate was placed in a tube (2 cm.×15 cm.) fitted with a ground glass joint. After the tube was constricted to facilitate sealing later, 15 ml. of anhydrous ether and 1.85 g. of methyl-d_3 bromide (13) were distilled into the tube, which was then frozen in liquid nitrogen, evacuated, and sealed. The reactants were heated to 85° C. in a rocking furnace for 20 hours.

Silver iodide was filtered off and washed with anhydrous ether. The residue, after removal of the ether, was distilled in a Späth bulb placed in an air furnace at 100° C. The yield of methyl-d_3 laurate was 3.5 g. (85.7%). It was a colorless liquid melting at + 10° C., n_D^{20} 1.4329.

For ordinary methyl laurate prepared in the same manner n_D^{20} was 1.4329.

Methyl 10-Undecynoate, $HC{\equiv}C(CH_2)_8CO_2CH_3$

10-Undecynoic acid was prepared as described in reference 10. Thirty grams of the acid were esterified with methanol and a trace of sulphuric acid under reflux for 4 hours. The ester had b.p. 69–71° at 1 mm., n_D^{20} 1.4465. Yield: 32 g.

Methyl 10-Dodecynoate, $CH_3C{\equiv}C(CH_2)_8CO_2CH_3$

The silver derivative of methyl 10-undecynoate was prepared by shaking overnight 10.0 g. of the ester with 170 ml. of ammoniacal silver nitrate solution (prepared by dissolving 8.5 g. of the salt in 100 ml. of water and adding ammonium hydroxide until the precipitate of silver oxide initially formed had just dissolved). Yield: 13.2 g. of product, m.p. 76–78° C. Calc. for $C_{12}H_{19}O_2Ag$, % Ag 35.6. Found: 35.2%.

The silver derivative (12.7 g.) was heated at 75° C. in a sealed tube overnight with 10.0 ml. of methyl iodide. The solids were filtered off in a gravity funnel and washed with ether. The residue, after removal of the ether by distillation, was distilled under vacuum from a Späth bulb in an air furnace at 85° C. Yield of product n_D^{20} 1.4529 was 4.0 ml. (45% of the theoretical).

10-Undecynoic Acid, $CH_3C{\equiv}C(CH_2)_8COOH$

The methyl ester was hydrolyzed by being heated on the steam bath for a few minutes with a slight excess of alkali in 50% ethanol–water. The solution was diluted with water and acidified at 0° C. with dilute hydrochloric acid. After one recrystallization from petroleum ether the acid melted at 51° C. Neutralization equivalent, calc. for $C_{12}H_{20}O_2$: 196; found: 198.

Methyl 10-Tridecynoate, $C_2H_5C{\equiv}C(CH_2)_8CO_2CH_3$

Eight grams of the silver derivative of methyl 10-undecynoate was heated with 4.0 ml. of ethyl iodide in a sealed tube overnight at 80° C. The reaction product was worked up and purified as described for the lower homologue. Yield: 1.2 g., n_D^{20} 1.4504.

Methyl 10-Decynoate-12-d_3, $CD_3C{\equiv}C(CH_2)_8CO_2CH_3$

The silver derivative of methyl 10-undecynoate was heated in a sealed tube with 6.7 ml. of methyl-d_3 iodide (13) overnight at 65° C. The product was isolated and purified as already described. Yield: 1.8 g. (50% of the theoretical) of ester, n_D^{20} 1.4514.

Methyl 12-Trichlorolaurate, $CCl_3(CH_2)_{10}CO_2CH_3$

A solution of 45 ml. of methyl 10-undecylenate in 75 ml. of chloroform containing 0.5 g. of dissolved dibenzoyl peroxide was heated in a pressure bottle for 4 hours at

110° C. in an oven; a further 0.5 g. of peroxide was added at the end of this time and heating was resumed overnight or for another 12 to 15 hours. The bulk of the chloroform was removed on the steam bath and the residue was distilled in a Vigreux column under reduced pressure (0.5 mm.). After collection of the unchanged methyl undecenoate at 65° C. the boiling point rose rapidly to 128–130° C. at 0.5 mm. and the trichloroester began to distill. Yield: 12.0 ml., n_D^{20} 1.4695.

Methyl Laurate-12-d_3, $CD_3(CH_2)_{10}CO_2CH_3$

(*a*) *By reduction of 10-dodecynoic acid with Raney nickel.*—10-Dodecynoic acid (1.0 g.) was dissolved in 200 ml. of 2% sodium hydroxide in water, and Raney nickel alloy (10.0 g.) was added in small portions over a period of 1 hour while the mixture was being heated on the steam bath. The hot solution was then filtered and the filtrate was acidified with dilute hydrochloric acid. The melting point of the acid which was filtered off was 42–43° C. The acid was converted into the methyl ester by heating the silver salt with methyl bromide as described above.

(*b*) *By zinc dust – deuterium oxide dechlorination.*—To a suspension of 14.0 g. of zinc dust (50% excess) in 150 ml. of anhydrous dioxane containing 30 ml. of deuterium oxide was added dropwise, with stirring, 15 g. of methyl trichlorolaurate. The reaction mixture was stirred overnight at 90° C. and under reflux for 4 hours. The reaction mixture was filtered and freed of dioxane by distillation under reduced pressure. The residue was taken up in ether and filtered from suspended solids. The filtrate was freed of ether and distilled in a Späth bulb yielding 8.2 g. (80.3% yield) of methyl laurate-12-d_3, n_D^{20} 1.4332.

The trichloro ester can also be dehalogenated with acetic acid-*d* and zinc dust with slightly higher yield but at the expense of preparing acetic acid-*d*.

Lauric-12-d_3 Acid, $CD_3(CH_2)_{10}COOH$

The acid was obtained by hydrolysis of the ester in nearly quantitative yield. Its infrared spectrum did not show the presence of a band for the CH_3 group at 1383 cm.$^{-1}$.

Lauric-12-d_3 Acid-d, $CD_3(CH_2)_{10}CO_2D$

This acid was prepared from the previous acid through the acid chloride.

Methyl-d_3 Laurate-12-d_3, $CD_3(CH_2)_{10}CO_2CD_3$

Silver laurate-12-d_3 prepared as described for the normal acid was heated with excess methyl-d_3 bromide in a sealed tube and the product was isolated as described in the case of methyl-d_3 laurate. The yield of distilled product, n_D^{20} 1.4337, was 92%.

Bromination of Lauric Acid

Attempts to brominate lauric acid under reflux in the presence of small amounts of phosphorus trichloride always resulted in the formation of α-bromolauric acid. No evidence of the presence of α-dibromolauric acid was ever found.

Brominations carried out at 140° C. in sealed tubes as described by Otto (15) likewise were unsatisfactory. Vast quantities of hydrogen bromide were evolved when the tubes were opened but the product boiled over a wide temperature range. Mixtures of dibrominated lauric acids were probably formed under these conditions. It is apparently not possible to introduce two bromine atoms in the α-position by this means.

Methyl 2,2-Dichlorolaurate, $CH_3(CH_2)_9CCl_2CO_2CH_3$

1-Decene (115 ml.), methyl dichloroacetate (177 g.), and 4.0 g. of dibenzoyl peroxide were heated for 15 hours on the steam bath. Unreacted decene and dichloroacetate ester were distilled off under 50 mm. pressure. After collection of a fraction (7.5 ml.) between

86° and 90° C. at 0.1 mm., methyl dichlorolaurate distilled over between 92° and 94° C. at 0.1 mm., n_D^{20} 1.4594, n_D^{23} 1.4584. The yield was only 28–30% but is offset by the ease of preparation of the ester.

Methyl Laurate-2,2-d_2, $CH_3(CH_2)_9CD_2CO_2CH_3$

Acetic acid-*d* was prepared as already described from acetyl chloride and deuterium oxide (16). To the acetic acid-*d* obtained from 26 ml. of acetyl chloride was added 6 g. of zinc dust and 5 ml. of methyl 2,2-dichlorolaurate. After the mixture had been stirred at room temperature overnight the zinc had nearly all turned white. The reaction mixture was poured into ice-water and extracted with 40 ml. of pentane. The residue, after removal of the pentane by distillation, was distilled in a Späth bulb. Yield: 3–6 g. of product, n_D^{22} 1.4342.

Reduction with deuterium oxide instead of acetic acid-*d* resulted in an impure product which showed unsaturation.

Lauric-2,2-d_2 Acid, $CH_3(CH_2)_9CD_2COOH$

The ester was hydrolyzed, isolated, and purified as described for lauric-12-d_3 acid. The yield was 2.9 g.

Lauric-2,2-d_2 Acid-d

This acid was prepared from lauric-2,2-d_2 acid via the chloride.

2,2-Dichlorolauroyl Chloride, $CH_3(CH_2)_9CCl_2COCl$

Dichloroacetyl chloride was prepared as described by Brown (1). The acid chloride (180 g.), decene-1 (53 ml.), and dibenzoyl peroxide (2.0 g.) were heated on the steam bath overnight. The reaction mixture was fractionated in a short Vigreux column under 0.06 mm. pressure. Unreacted decene and dichloroacetyl chloride were collected up to 80° C. 2,2-Dichlorolauroyl chloride then distilled at 82–83° C. Yield: 6.0 ml., n_D^{20} 1.4629.

The amide was prepared by treating a sample of the chloride with ammonia and dilute ethanol. After one recrystallization from ethanol the amide melted at 62–64° C.

2,2-Dichlorolauric Acid, $CH_3(CH_2)_9CCl_2COOH$

A mixture of 1 ml. of 2,2-dichlorolauroyl chloride and 5 ml. of water was stirred overnight at room temperature and extracted with ether. The ether solution was dried over anhydrous sodium sulphate and distilled. The residue which remained was distilled in a Späth bulb. The distillate was a colorless liquid with an odor of lauric acid. Its neutralization equivalent was somewhat low.

Methyl-d_3 Laurate-2,2-d_2, $CH_3(CH_2)_9CD_2CO_2CD_3$

The silver salt was prepared as has already been described for ordinary lauric acid and lauric-12-d_3 acid. Methyl-d_3 laurate-2,2-d_2 was prepared from the silver salt and methyl-d_3 bromide as described above.

Diethyl n-Decylmalonate, $CH_3(CH_2)_9CH(CO_2C_2H_5)_2$

"Molecular" potassium (2.0 g.) was prepared in xylene dried over sodium (21), and washed three times by decantation with absolute ether. It was then covered with 40 ml. of absolute ether and anhydrous ethanol (2.8 ml., dried by distillation over magnesium ribbon) was added. The reaction mixture was heated for 4 hours under reflux. Diethyl oxalate (9.4 ml.) and methyl laurate (9.2 ml.) were added to the ice-cold suspension of potassium ethoxide in ether. After 25 hours' stirring the reaction mixture was poured into ice-water containing a little hydrochloric acid. The ether was separated, washed

three times with water, and dried over anhydrous sodium sulphate. The ether was removed at the ordinary pressure and the residue decarboxylated by heating under vacuum at 150° C. until no further evolution of gas took place. The product began to reflux as the pressure fell to 0.5 mm. The yield of product, n_D^{20} 1.4364, b.p. 120–124° C., was 9.0 ml.

Floyd and Miller (4) report b.p. 155–158° C. at 3 mm. and n_D^{25} 1.4353 for *n*-decylmalonic ester.

n-Decylmalonic-2-d Acid-d$_2$, $CH_3(CH_2)_9CD(CO_2D)_2$

Sodium deuteroxide was prepared by adding 7.0 g. of clean sodium in small portions to 50 ml. of deuterium oxide stirred under an atmosphere of dry nitrogen. *n*-Decylmalonic ester was then added and the reaction mixture was stirred overnight just below the boiling point. The solution was acidified by addition of deuterium sulphate until strongly acid, and extracted with ether. On evaporation of the ether, 6.1 g. of white solid melting at 111–113° C. was obtained. According to Wallingford (22) *n*-decylmalonic acid melts at 118–119°. Recrystallization of the acid from chloroform raised its melting point to 116° C. The deuterated acid could be expected to melt at a lower temperature than the normal one (24).

Heating above its melting point converted the *n*-decylmalonic-d_2 acid-d_2 into lauric-2,2-d_2 acid-*d*.

Diethyl n-Decylmalonate-10-d$_3$, $CD_3(CH_2)_9CH(CO_2C_2H_5)_2$

A Claisen condensation between diethyl oxalate and methyl laurate-12-d_3 was carried out exactly as just described. From 9.3 g. of laurate ester there was obtained 9.3 ml. of malonic ester, n_D^{20} 1.4373. Hydrolysis gave 6.1 g. of acid, m.p. 111–113° C.

Lauric-2,2,12,12,12-d$_5$ *Acid-d*, $CD_3(CH_2)_9CD_2CO_2D$

This acid was obtained by decarboxylating the corresponding malonic acid in a glycerine bath at 140° C.

Methyl Laurate-2,2,12,12,12-d$_5$, $CD_3(CH_2)_9CD_2CO_2CH_3$

Silver laurate-2-2,12,12,12-d_5 was prepared as already described for the normal acid. It was converted into the ester by heating with methyl iodide, also as described above.

Methyl-d$_3$ *Laurate-2,2,12,12,12-d*$_5$, $CD_3(CH_2)_9CD_2CO_2CD_3$

This ester was prepared by the methods described above.

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ELECTROLYTIC CONDUCTANCE IN HYDROGEN PEROXIDE – WATER MIXTURES

PART I. THE ALKALI CHLORIDES[1]

D. K. THOMAS[2] AND O. MAASS

ABSTRACT

The equivalent conductance of a series of alkali chlorides has been measured in water – hydrogen peroxide mixtures over the whole range of solvent composition. The measurements were made by a simple direct-current method, and the results obtained are interpreted in terms of the viscosity of the solvent.

INTRODUCTION

The close similarity in the values of certain of the physical constants for water and hydrogen peroxide has been appreciated for some time, and in some instances extensive studies of their variation in mixtures of the two compounds has been carried out (1, 2, 3, 4). In all cases these similarities have received adequate explanation in terms of the possession by both molecules of structures adapted to strong hydrogen bonding.

Mixtures of hydrogen peroxide and water have been found to display non-ideality in that

(*a*) there is a volume change on mixing (3),

(*b*) there is a finite heat of mixing (4),

(*c*) the vapor pressures of the solutions do not obey Raoult's law (5).

The direction of these departures from ideality is interpreted as indicating an enhancement of either the number or the force of the attractions between molecules upon forming the solutions.

One of the least-studied aspects of the hydrogen peroxide – water system has been that of its behavior as an ionizing medium, this possibly being due to the difficulty, until fairly recently, of obtaining concentrated hydrogen peroxide of a high degree of purity. Recently, measurements (6, 7) of the conductivities of a few acids and salts in solvents of compositions ranging from 100% water to 100% hydrogen peroxide have been made. In all cases it appears that addition of hydrogen peroxide to water brings about a marked reduction in the electrical conductance, and furthermore, a point is reached at which the conductance of an acid is lower than that of its potassium salt (7). No completely adequate explanation has been forthcoming to account for these results.

In the present work an attempt has been made to carry out a comprehensive study of the alkali chloride series in solvents of composition varying from 100% water to 98% hydrogen peroxide, with the object of

(*a*) seeing whether the conductance trends displayed in aqueous solution are maintained,

(*b*) attempting to account for the variation in conductance with solvent composition.

EXPERIMENTAL

The use of hydrogen peroxide as a solvent for conductivity work is beset with one major difficulty, namely its tendency to decompose at room temperature in the presence of only minute quantities of impurity. Even in the apparent absence of any catalyst sufficient

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decomposition may occur to render a conductance measurement extremely inaccurate.

All the results subsequently quoted were obtained by the use of a very simple direct-current method, in which the potential difference between two points in the solution, as measured by a pair of probe electrodes, was balanced against that across a standard resistance placed in series with the conductivity cell. This method is identical in principle to that used for the measurement of the conductance of aqueous solutions of alkali halides by Brönsted and Nielsen (8), Gunning and Gordon (9), and more recently by Ives and Swaroopa (10), and Lim (11). In the hands of these workers this direct-current method has been shown to give results closely similar to those obtained on the same systems by the use of the alternating-current method. In fact, Gunning and Gordon found that in dilute solution the results obtained from the two methods agreed to within the apparent precision of either set of measurements.

The conductivity cells used were of Pyrex glass construction, the probe electrodes and the current-carrying electrodes being molded from pure tin. All solutions were made by weight from the pure constituents and, because of their inherent instability, were used immediately. The cell constants were determined using aqueous potassium chloride solutions of concentrations 0.01 *N*, 0.05 *N*, and 0.10 *N*.

A typical set of values was as follows:

(*a*) $c = 0.01$, $K = 361.0$;
(*b*) $c = 0.05$, $K = 361.4$;
(*c*) $c = 0.10$, $K = 361.1$.

The cells were immersed in a thermostat controlled to ±0.01° C. during all observations, and balance between the solution and the standard resistance was obtained by varying the latter until identical readings were obtained on a Keighley model 210 electrometer.

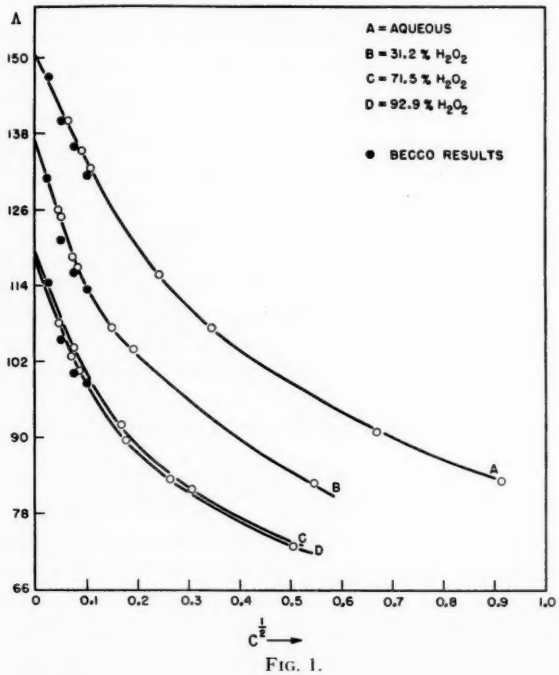


FIG. 1.

Before proceeding with the main series of measurements a study was made of the system K_2SO_4–H_2O_2–H_2O in order that a comparison could be made between the precision of the a-c. method as used by Shanley *et al.* (6, 7) and the d-c. method used in these investigations. As will be seen from Fig. 1, both methods lead to essentially the same result over the whole range of solvent composition. At the lower concentrations a solvent correction of the form $K_{\text{solute}} = K_{\text{solution}} + K_{\text{solvent}}$, where K signifies specific conductance, was applied.

It was found that the reproducibility in all the solvents used was always as good as 1%.

MATERIALS

(*i*) *Alkali Chlorides*

The alkali chlorides, i.e. those of lithium, sodium, potassium, rubidium, and cesium, were all high-grade analytical reagents, each containing only trace quantities of other alkali metals. They were dried by prolonged heating at 120° C. and stored in a desiccator until required.

(*ii*) *Hydrogen Peroxide*

Becco Chemicals 98% hydrogen peroxide was used throughout. Solvents of lower peroxide concentration were made by dilution of the concentrated material with water of specific conductance 1.5×10^{-6} mhos, and were standardized volumetrically with potassium permanganate.

(*iii*) *Tin*

The probe electrodes and current-carrying electrodes were made from pure tin, the maximum limits of impurity being as follows: As, 0.0003%; Cu, 0.002%; Te, 0.005%; Pb, 0.010%.

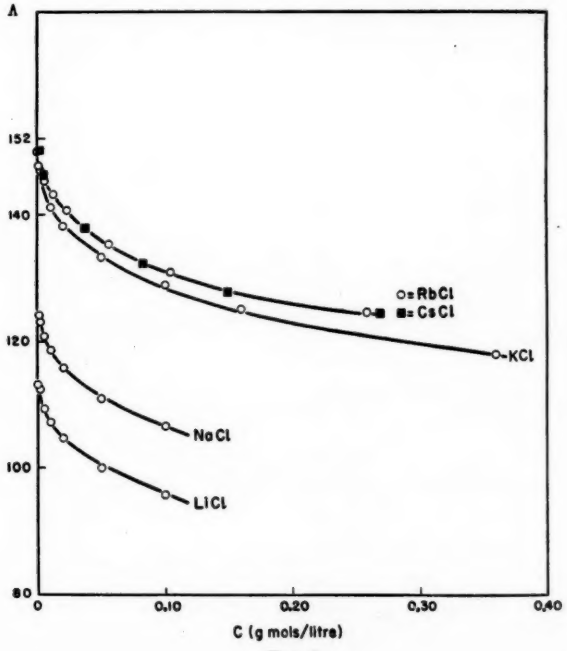


FIG. 2.

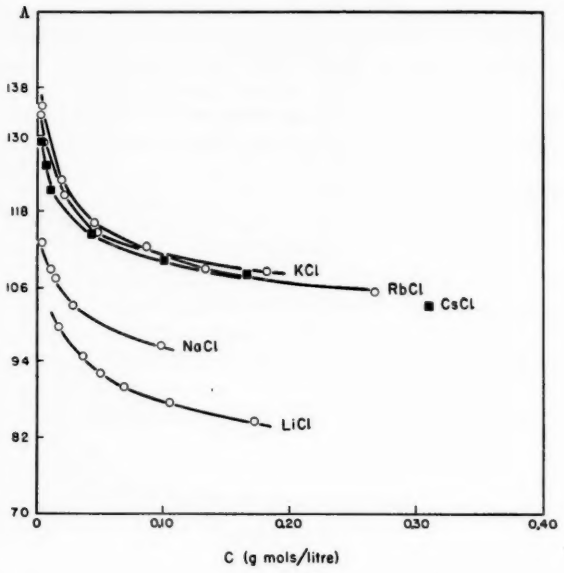

Λ
138
130
118
106
94
82
70
0
0.10
0.20
0.30
0.40
KCl
RbCl
CsCl
NaCl
LiCl
C (g mols/litre)

FIG. 3.

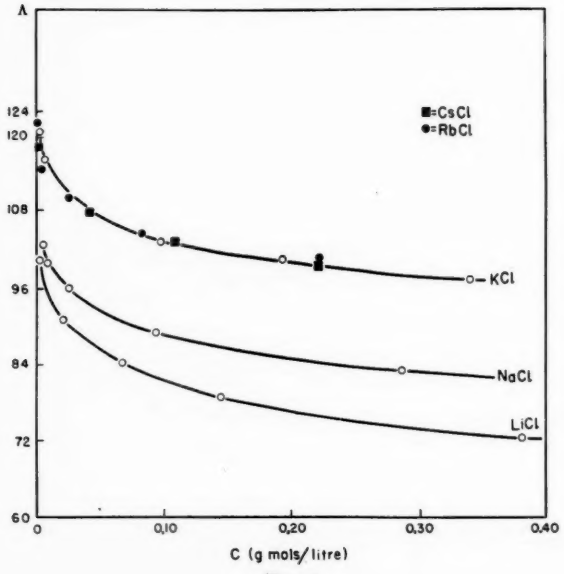
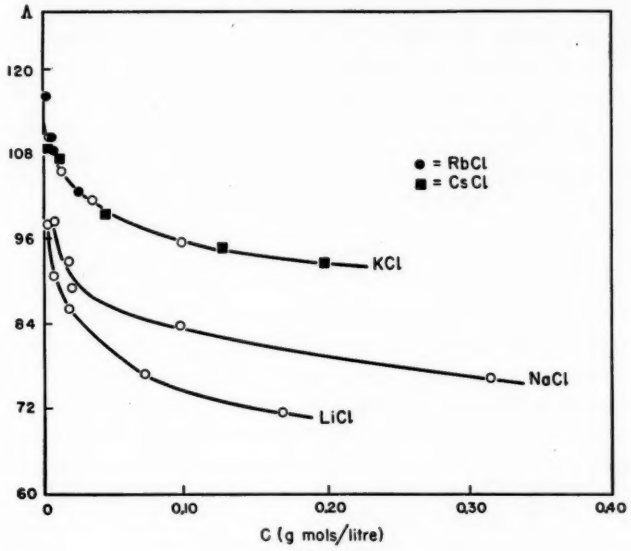

Λ
124
120
108
96
84
72
60
0
0.10
0.20
0.30
0.40
■=CsCl
●=RbCl
KCl
NaCl
LiCl
C (g mols/litre)

FIG. 4.


Λ
120
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96
84
72
60
0
0.10
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● = RbCl
■ = CsCl
KCl
NaCl
LiCl
C (g mols/litre)

FIG. 5.

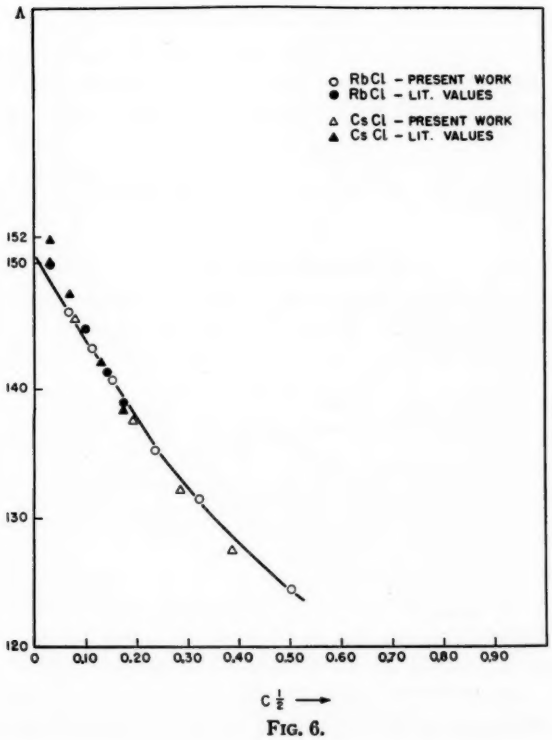
Λ
○ RbCl – PRESENT WORK
● RbCl – LIT. VALUES
△ CsCl – PRESENT WORK
▲ CsCl – LIT. VALUES
152
150
140
130
120
0
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
C ½ ⟶

FIG. 6.

RESULTS

The results obtained are presented graphically in Figs. 2–6. Except in the cases of rubidium and cesium chloride the data for aqueous solution were obtained from the literature; for these two the only available data were those due to Boltwood (12) and Bredig (13). Since these showed the curves for equivalent conductance against concentration to cross at $C^{1/2} = 0.125$ it was felt that confirmation of these results would be in order. The measurements made did, in fact, substantiate these early observations, but deviated from them slightly at low concentration to give a value of Λ_0 different by 0.5% (see Fig. 6).

In all cases a solvent correction was applied at the lowest concentrations.

DISCUSSION

Reference to the results shows that the addition of hydrogen peroxide to the system alkali chloride – hydrogen peroxide – water leads to a reduction in the equivalent conductance of the solution. This is in accord with previous observations (6, 7). The greatest changes are effected by adding H_2O_2 to solutions containing a high percentage of water, and, in fact, once the H_2O_2 concentration exceeds about 75% by weight, further addition leads to only very small changes in conductance. A curve showing the variation of equivalent conductance with the percentage of H_2O_2 for KCl solutions is reproduced in Fig. 7, and this displays a behavior typical of all the alkali chlorides.

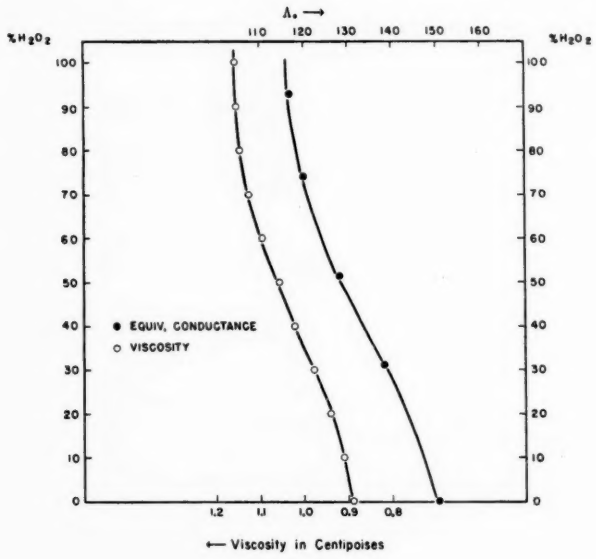

FIG. 7.

It will be seen that the sequence of conductivity values is the same as that in aqueous solution insofar as lithium chloride has the lowest value and sodium chloride the next lowest. The chlorides of potassium, rubidium, and cesium lie rather close to each other in aqueous solution, and addition of hydrogen peroxide appears to bring them even closer together until eventually, as in 98% peroxide, they are indistinguishable.

There seems little doubt that, in hydrogen peroxide as in water, the ions are solvated and that in concentrated hydrogen peroxide the relative degrees of solvation for the cations are Li > Na > K $\simeq$ Rb $\simeq$ Cs. At what particular stage the hydrogen peroxide begins to replace the water in the solvation sheath remains a matter for conjecture, but there seems good reason to suppose that, in view of its much higher dipole moment (14), there would be a tendency for this to occur. This view is supported by the work of Gorin (15), who observed a 'salting-in' of hydrogen peroxide in a number of aqueous solutions of electrolytes. Further reference to Fig. 7 shows the similarity in the variations of equivalent conductance, and of viscosity, with the percentage by weight of hydrogen peroxide in the solvent. This suggests that viscosity change is responsible for the conductance change. If that is the case, and assuming the applicability of Stokes' law to the solvated ions, the product $\Lambda_0\eta$ should be a constant. That this is indeed so may be seen by reference to Table I. The viscosity data in Table I are those of Shanley *et al.* (16).

TABLE I

Wt.% H_2O_2	Viscosity in centipoises	LiCl		NaCl		KCl		RbCl		CsCl	
		Λ_0	$\Lambda_0\eta$	Λ_0	$\Lambda_0\eta$	Λ_0	$\Lambda_0\eta$	Λ_0	$\Lambda_0\eta$	Λ_0	$\Lambda_0\eta$
0	0.00895	114.7	1.02	127.0	1.14	150.4	1.34	150.5	1.35	153.0	1.37
31	0.00970	107.8	1.05	116.6	1.13	138.0	1.33	140.0	1.36	131.2	1.27
52	0.01055	101.2	1.07	106.9	1.12	128.4	1.35	121.0	1.28	118.0	1.25
75	0.01132	99.0	1.12	102.0	1.15	117.4	1.36	117.2	1.33	108.0	1.22

CONCLUSION

The conductivity trends shown by the alkali chlorides in pure water are to a large extent maintained in hydrogen peroxide – water mixtures, and in pure hydrogen peroxide it appears that the relative degree of solvation of the alkali metal cations is Li > Na > K $\simeq$ Rb $\simeq$ Cs.

The decrease in conductance for all these salts in passing from a solvent of lower to one of higher peroxide concentration is accounted for in terms of the accompanying increase in viscosity.

ACKNOWLEDGMENTS

Thanks are due to Becco Chemicals for a gift of the hydrogen peroxide, and for valuable discussion in the early stages of the work; and to Mr. Gordon Graham for invaluable technical assistance.

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A STUDY OF THE CONDUCTIVITY OF CERTAIN ACIDS AND ALKALI HALIDES IN GLYCOL AND THE INFLUENCE OF THE ADDITION OF A SECOND SOLVENT[1]

P. KIRBY[2] AND O. MAASS

ABSTRACT

The conductivities of HCl, H_2SO_4, HNO_3, and a number of their alkali metallic salts were measured in ethylene glycol. The influence of the addition of water, methanol, and hydrogen peroxide was determined. The results are discussed on the basis of well-known theories of electrolytic conductivity involving H^+ ions.

INTRODUCTION

The conductivity of various halogen acids and alkali halides in methyl and ethyl alcoholic solutions has been studied by Goldschmidt and co-workers, and although generally the results obtained were predictable on the basis of prevailing conductivity theories, anomalous results were found on the addition of small quantities of water to the acidic solutions (1).

It was found that water gave an initial diminution of conductivity until a minimum was reached after the addition of between 1 and 2 moles of water per liter. Continued addition of water then produced a steady rise in conductivity. Similar results were found later for the addition of water to solutions of strong acids in alcoholic solution by Murray-Rust and Hartley (2), and Beznan and Verhoek (3).

Goldschmidt and Aarflot (4) also studied the effect of the addition of small quantities of methyl alcohol to an ethanolic solution of HCl, but found that it "hardly affected" the conductivity.

The present investigation describes a series of similar conductivity determinations on hydrochloric acid and alkali halides in ethylene glycol. Small quantities of water were added to both the acidic and salt solutions, and the acidic solutions showed a decrease in conductivity similar to that found by Goldschmidt and Dahll (1), although the range of water content over which this diminution was observed was much wider than that found for the solutions of acids in methanol. It was also found that addition of methanol to the solutions studied gave no decrease in conductivity. The conductivity of H_2SO_4 in glycol was decreased, however, by the addition of hydrogen peroxide.

EXPERIMENTAL

The direct-current method of conductivity determination was used in this work. The apparatus consisted of a conductivity cell, 90 v. dry cell, resistance box, and reversing switch in series. In addition, the potential difference across either the probe electrodes of the conductivity cell or the resistance box of the main circuit could be placed on the needle of a modified gold-leaf electroscope, by means of a two-way switch.

The electroscope consisted of a pair of brass plates at a separation of $\frac{1}{2}$ in., with a steady 90 v. across them; a charge could then be placed onto a gold-wire needle and the displacement observed by a microscope through a transparent window.

[1]*Manuscript received October 23, 1957.*
Contribution from the Division of Pure Chemistry, National Research Laboratories, Ottawa, Canada. Issued as N.R.C. No. 4613.
[2]*N.R.L. Postdoctorate Fellow.*

The electroscope was used as a null-point instrument, i.e. the metallic resistance in the conductivity circuit was varied until the same displacement of the needle was given by (and hence the same potential difference existed across) both the resistance box and the probes of the conductivity cell. This instrument had the great advantage of a high resistance (air gap); hence no current was drawn from the probe electrode circuit when placed across the electroscope. This in turn means that negligible polarization occurred at the probe electrodes themselves.

The conductivity cell had a capacity of 300 cc., the cell constant being determined by using three different concentrations of potassium chloride solution (four determinations were made at each of the concentrations 0.01 *N*, 0.002 *N*, and 0.001 *N*; at each concentration the agreement was within 1%; the over-all agreement was also within 1%). Using the conductivity values of Shedlovsky (5) for potassium chloride the cell constant was found to be 2.300 ± 0.003 cm.$^{-1}$. The electrodes and probes used in the conductivity cell were all of platinum.

The ethylene glycol used was reagent-grade Eastman-Kodak material ($n_4^{22} = 1.4313$). The hydrochloric acid was anhydrous and was added as a gas. The weight added was determined by a pressure-difference technique involving the freezing out of the gaseous material into a small bulb and then the evaporation of it directly into the solution.

In the nitric acid determinations, fuming nitric acid was used ($HNO_3 = 89.5\%$), but here, as with the sulphuric acid estimations ($H_2SO_4 = 96\%$), the amount of water added with the solute is so small that its effect on the conductivity of the system can be considered negligible ($\sim 0.05\%$ of the volume of solvent taken). A 0.05 *N* solution of HNO_3 in glycol was made up and allowed to stand for 7 days. During this time 25-ml. samples were withdrawn from time to time and titrated against 0.1 *N* sodium hydroxide solution. The titer was found to remain steady throughout the seven days. A similar result was obtained when 5% aqueous glycol was used as the solvent.

It was shown, therefore, that no reaction occurs between HNO_3 and ethylene glycol during the course of the conductivity determinations, which are of the duration of 45 minutes.

Hydrochloric acid was also found to give no chemical reaction with glycol by the same method.

EXPERIMENTAL RESULTS

The experimental work carried out can be divided into two sections: one, the determination of limiting values of conductivities of certain acids and salts in ethylene glycol; the other, the effect of addition of small quantities of a second solvent on the conductivity of various solutions in ethylene glycol.

As a preliminary to this work, the conductivity of ethylene glycol itself was determined and was found to be 1.28×10^{-7} cm.$^{-1}$. (Previous value recorded (6) is 2.4×10^{-7} cm.$^{-1}$.)

The authors' value was used as a solvent correction in the determination of Λ_0 for HNO_3, KNO_3, and $NaNO_3$. The values of Λ_0 to be derived by extrapolation to zero concentration of the conductivity values are determined from Table I.

The corrected values of Λ_0 found at 25° C. for these compounds are recorded in Table II. Owing to extrapolation, the accuracy of Λ_0 is a good deal less than the 1% claimed for the experimental determination, but should be within 3%.

In Table II the values for Λ_0 are given for glycol solutions. Also, for comparison, those in water (5), methanol (6), and ethanol (6) are given in Table II. It is interesting to

TABLE I

THE VARIATION OF Λ_c (CM.$^{-1}$) WITH $\sqrt{c}$ (G-MOL./LITER)$^{\frac{1}{2}}$

HNO_3		KNO_3		$NaNO_3$	
$\sqrt{c}$	Λ_c	$\sqrt{c}$	Λ_c	$\sqrt{c}$	Λ_c
0.0183	28.4	0.0104	9.43	0.0151	7.49
0.0272	27.8	0.0201	9.27	0.0279	7.35
0.0368	27.0	0.0307	8.95	0.0438	7.29
0.0538	25.7	0.0425	8.80	0.0539	7.23
0.100	22.2	0.0540	8.73	0.0642	7.19
		0.0635	8.54		

note that the conductivities of the salts are much lower compared with nitric acid in glycol than is the case in either methanol or ethanol. Glycol, in fact, gives a relationship similar to that given by water.

TABLE II

CORRECTED VALUE OF Λ_0

Comp.	Glycol	Water	MeOH	EtOH
HNO_3	29.8	421	203	88
$NaNO_3$	7.6	121	107	47
KNO_3	9.6	145	115	50

The remaining results can best be illustrated by means of Figs. 1–6; in all these figures specific conductivity has been plotted against concentration, as it was considered that this best illustrated the effects under examination.

Fig. 1 shows the effect of the addition of water to solutions of hydrochloric acid in ethylene glycol and Fig. 2 is derived from this to illustrate the effect over the range of

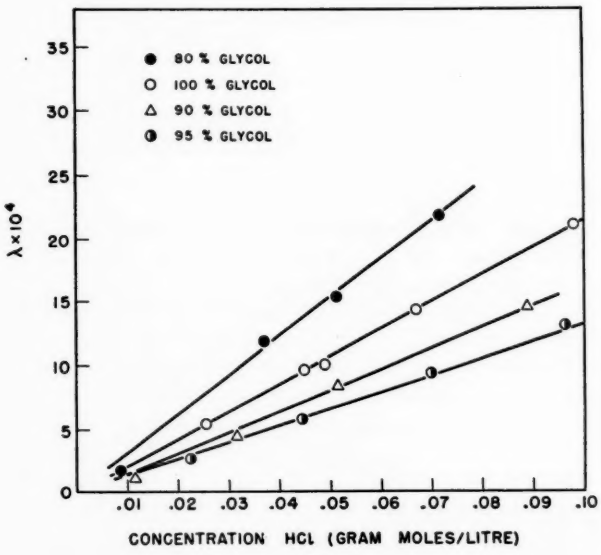

FIG. 1.

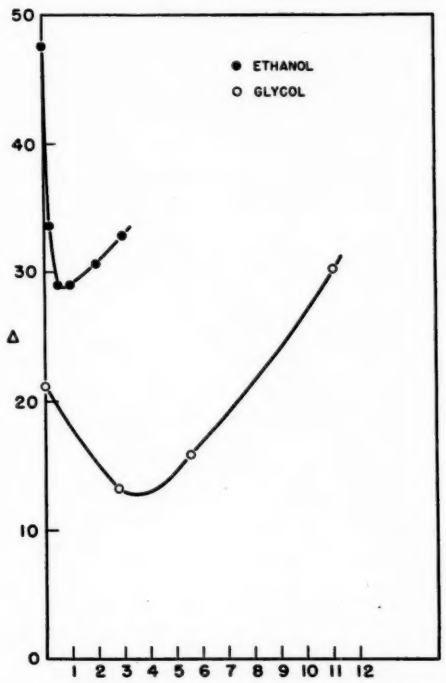
ETHANOL
GLYCOL
Δ
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12
CONCENTRATION WATER (GRAM MOLES/LITRE)

FIG. 2.

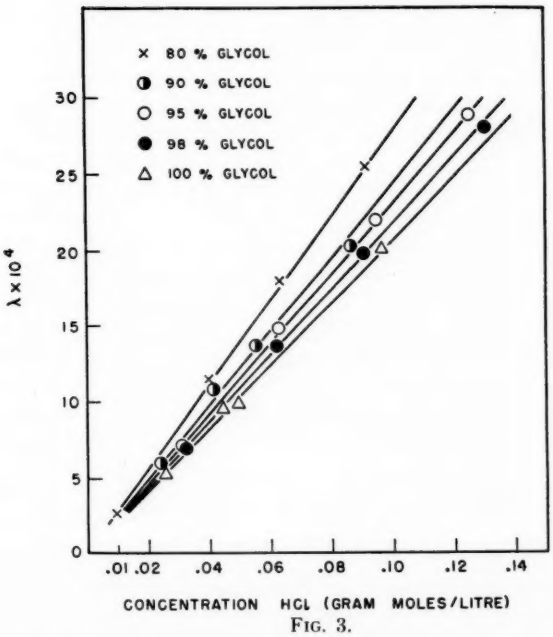
80 % GLYCOL
90 % GLYCOL
95 % GLYCOL
98 % GLYCOL
100 % GLYCOL
λ x 10⁴
30
25
20
15
10
5
0
.01 .02 .04 .06 .08 .10 .12 .14
CONCENTRATION HCl (GRAM MOLES/LITRE)

FIG. 3.

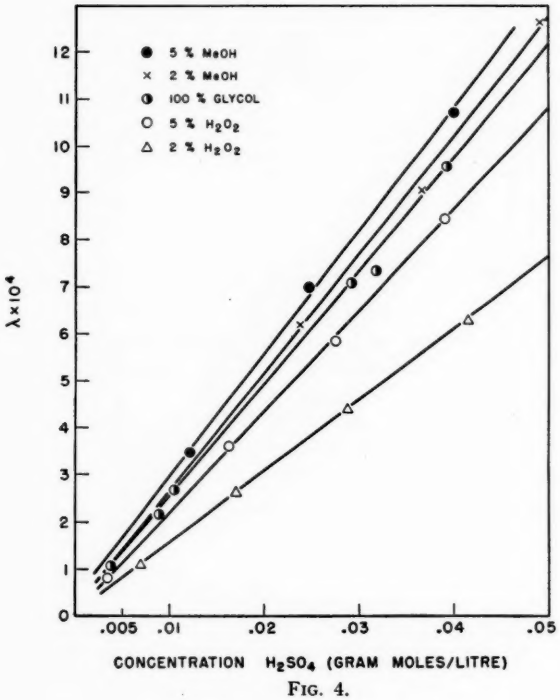
5 % MeOH
2 % MeOH
100 % GLYCOL
5 % H_2O_2
2 % H_2O_2
$\lambda \times 10^4$
CONCENTRATION H_2SO_4 (GRAM MOLES/LITRE)

FIG. 4.

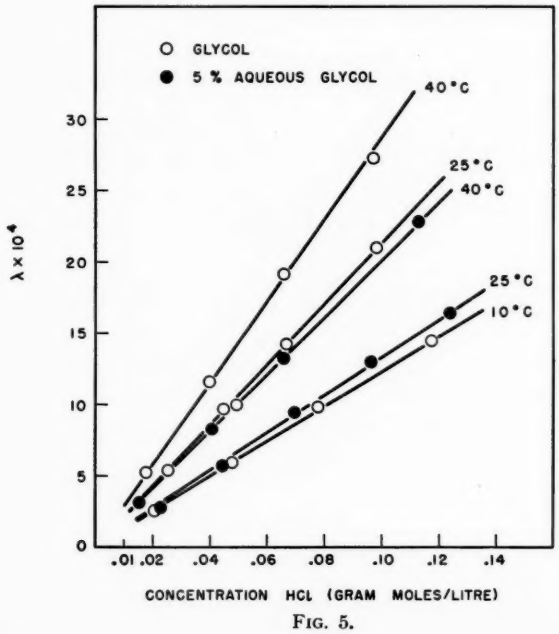
GLYCOL
5 % AQUEOUS GLYCOL
40 °C
25 °C
40 °C
25 °C
10 °C
$\lambda \times 10^4$
CONCENTRATION HCl (GRAM MOLES/LITRE)

FIG. 5.

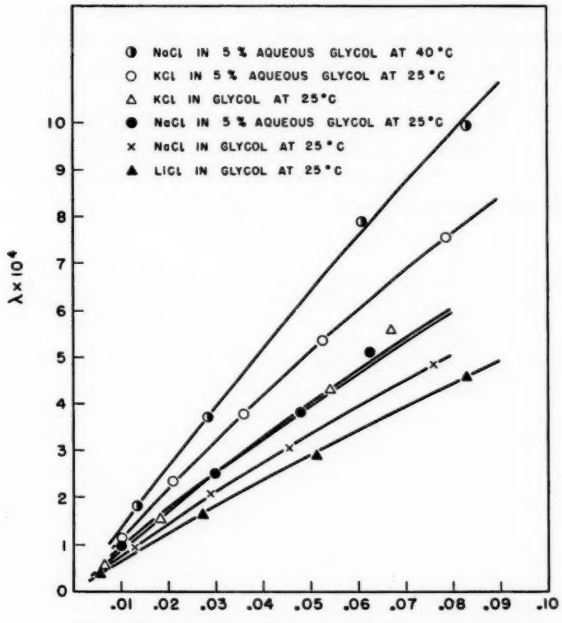

FIG. 6.

water content 0–10 g-mol./liter for a solution containing 0.05 g-mol. HCl/liter. Also in Fig. 2 is shown the curve obtained by Goldschmidt (1) for the addition of water to a solution of 0.05 g-mol. HBr/liter in ethanol. It was found that the diminution effect was much more gradual in glycol and also was evident over a much greater range of water content, although the over-all fall in conductivity was similar in either case.

Fig. 3 illustrates the effect of the addition of methanol to a glycolic HCl solution. It can be seen that an increase in conductivity was found roughly proportional to the amount of methanol added.

Fig. 4 shows the resultant conductivities for the addition of water, 98% hydrogen peroxide, and methanol to a glycolic solution of sulphuric acid. Both water and hydrogen peroxide produce a reduction of conductivity but that produced by hydrogen peroxide is less than that of water. Again, a steady increase was found on addition of methanol.

Fig. 5 deals with the temperature coefficients of hydrochloric acid both in glycol and in 5% aqueous glycol. A temperature coefficient of 2% per ° C. increase was found for the glycol solution over the range of temperature covered (25°–40°), whereas that of the 5% aqueous glycol solution was 2.3% per ° C. over the same temperature range.

Fig. 6 gives the conductivity values found for the alkali metal chlorides again in both glycol and 5% aqueous glycol at 25° C. The order of conductivity was $K^+ > Na^+ > Li^+$. The curve for NaCl in 5% aqueous glycol at 40° C. is also shown. Sodium chloride was found to have a temperature coefficient of 2.4% per ° C. between 25° and 40° C. in 5% aqueous glycol.

DISCUSSION OF RESULTS

Previous workers on the diminution of the conductivity of solutions of hydrochloric acid in organic solvents by the addition of water have always taken as a basis of their

interpretation of these results the greater stability of the H_3O^+ ion than that of the corresponding ROH_2^+ ion (1, 9, 11), which results in a certain degree of fixing of the proton, causing it to be less available as a charge carrier in slightly aqueous solutions of acids than it is in the solution of an acid in the pure solvent.

More recently a survey of the subject has been made by Conway, Bockris, and Linton (10), who suggest that the addition of water molecules to a proton-containing alcoholic solution presents an alternative route for the protons through the solution. The protons may now go to the H_2O molecules and a study of the equilibrium constants for the changes

$$H_3O^+ + ROH \rightleftharpoons ROH_2^+ + H_2O,$$

where R = Me, Et, or *n*-Pr, indicates that as soon as a trace of water is present nearly all the protons form H_3O^+ ions, and that the reverse process is improbable since it would require an increase in free energy.

When a trace of water is added to a solution of an acid in an alcoholic solution, not only are the protons mainly incorporated into the H_3O^+ ions, but so are the added water molecules. Thus proton exchanges between H_3O^+ and H_2O molecules will be infrequent owing to the smaller number of H_2O molecules present. The H_3O^+ ion rather than being involved in the transfer of protons along a chain of water molecules, as is present in aqueous solutions, will tend to remain as an independent ion, and it could be predicted that it should behave like the similarly sized K^+ ion.

To examine this prediction KCl and HCl were each studied in 0.05 g-mol./liter solution at 25° C., in a solvent of ethylene glycol containing 2.8 g-mol. water/liter, and the conductivity values were as follows:

Solvent	HCl	KCl
Aq. glycol	13.2	10.2
Water (7)	415.8	143.5
Glycol	21.2	8.1

The values for water and glycol are also given where the conductivity values are far more divergent. Further evidence for the presence of free H_3O^+ ions in solutions of acids in ethylene glycol containing small quantities of water was obtained by studying the temperature coefficients. A conductance mechanism involving proton transfer along a chain of glycol molecules should be far less sensitive to temperature than is a conductance caused by the movement of ions, since in the former case any acceleration caused by exciting the particles will be offset by the breakdown of the chain, whereas in the latter case the particles will move more quickly.

Conductivity determinations were carried out for hydrochloric acid and sodium chloride in 5% aqueous glycol at 25° C. and 40° C. and the temperature coefficients were determined.

The values are given in Table III together with those found for HCl in both glycol and water. It was found that the temperature coefficient for the conductivity of HCl was greater in 5% aqueous glycol than in either glycol itself or water; also the temperature coefficient in 5% aqueous glycol was similar to that found for NaCl in the same solvent.

Figure 2 illustrates that the decrease in conductivity found in proton-containing glycolic solutions occurred over a much larger range of water content than that found for solutions of acids in ethanol: This is no doubt a viscosity effect. In the more viscous

TABLE III

	Solvent	$A_{0.5}$ 25°	$A_{0.5}$ 40°	% dec./° C.
NaCl	5% aq. glycol	8.0	12.7	2.4
HCl	5% aq. glycol	13.2	20.1	2.3
HCl	Glycol	21.2	28.6	1.8
		25°	35°	
HCl	Water	399.09 (7)	460 (12)	1.3

glycol solution the chance of a collision between an H_3O^+ ion and a free water molecule will be much less than that in alcohol as the velocity of both particles will be reduced. Hence a minimum conductivity value is found for a 0.05 *N* solution of HBr in ethanol at 0.7 g-mol. water/liter, whereas a 0.05 *N* solution of HCl in ethylene glycol has 3.5 g-mol./liter water for a minimum conductivity.

In the runs where methyl alcohol was added to glycolic hydrochloric acid solution no decrease in conductivity was obtained. In fact, the addition seemed to produce a steady increase in conductivity dependent upon the amount of alcohol added. On the basis of previous theory this would indicate that the protons in a methanol – ethylene glycol mixture can attach themselves equally well to either type of molecule and the proton exchange mechanism is not affected.

It is interesting to note, however, that addition of hydrogen peroxide does give a decrease in conductivity. This was a considerably smaller effect than that given by water but does indicate the comparative stability of the $H_3O_2^+$ ion.

With regard to the conductivity of the alkali halides in both glycol and 5% aqueous glycol solution the order of conductivity $K^+ > Na^+ > Li^+$ is found. Thus it would seem reasonable to suppose that in both solvents solvation occurs, as the size of the unsolvate ions is in the opposite direction.

Addition of water to the alkali halide solutions in glycol gives also a steady increase in conductivity.

CONCLUSIONS

A study of the conductivity of various acids and alkali halides in solutions of glycol and aqueous glycol has shown that the behavior of these solutions supports the present theories of the diminution of conductivity caused by the addition of small amounts of water to alcoholic solution.

It was also shown that a similar, although smaller, effect was also produced by the addition of small amounts of hydrogen peroxide to acidic solutions in glycol. In the case of addition of methyl alcohol, no diminution in conductivity was observed and it was considered that this was due to the instability of the OH_2^+ ion.

To recapitulate, it is accepted that the relatively large conductivity of acids in aqueous solution is due to the formation of an H_3O^+ ion, where the proton, without any significant change in energy, can pass from one water molecule to another. While this movement from water molecule to water molecule does not involve any great change in energy, it is still recognized that the proton is always held as an H_3O^+ ion by a water molecule.

The high conductivity of acids in aliphatic alcohols is explained in a similar way, but the proton is not held so firmly in the ROH_2^+ ion. The addition of water to a solution of this type may actually decrease the conductivity because the water molecule capturing

the proton is not apt to pass it on to organic molecules as easily. It is thus taken out of circulation except insofar as it acts as a free ion. With the continued addition of water the opportunity of the proton to pass from water molecule to water molecule increases with the result that the conductivity eventually will again increase.

ACKNOWLEDGMENT

To Mr. G. Graham the authors wish to record their indebtedness for the valuable technical assistance given during the course of this research.

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12. JONES, H., *et al.* Carnegie Inst., Washington, Publ. No. 17, p. 12.

NITRIMINO-(1H)PYRIDINIUM AND NITRIMINO-(3H)THIAZOLIUM INNER SALTS

THE STRUCTURE OF SOME NITRIMINES IN THE LIGHT OF INFRARED STUDY[1]

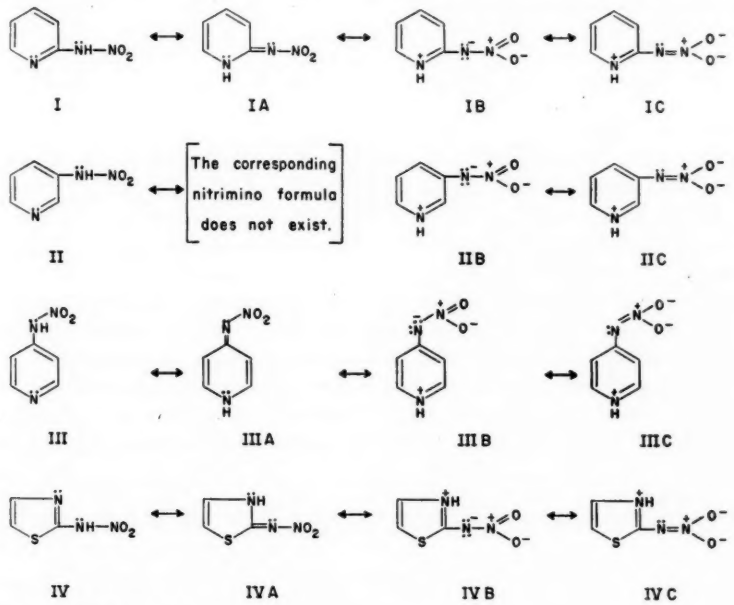
ALFRED TAURINS

ABSTRACT

Compounds previously known as nitraminopyridines and 2-nitraminothiazoles are formulated as nitrimino-(1H)pyridinium and 2-nitrimino-(3H)thiazolium inner salts on the basis of the infrared study. In the solid state, the three isomer nitriminopyridines do not exhibit any infrared absorption of the —NH group in the region 3400–3200 cm.$^{-1}$ but show a wide band at lower frequencies in the region 2880–2550 cm.$^{-1}$. 2-Nitriminothiazole shows only a wide band between 3140 and 2270 cm.$^{-1}$. These shifts of absorption bands can be correlated with structures derived from the classical nitrimino tautomeric forms in which the resonance effect stabilizes (1H)pyridinium and (3H)thiazolium cations, and a nitrimino group carrying a negative charge. *n*-Butylnitramine, a non-resonating compound, absorbs strongly at 3300 cm.$^{-1}$, indicating that nitramino groups are not associated.

INTRODUCTION

The nitration product of 2-aminopyridine reacts in two tautomeric forms, 2-nitramino- (I) and 2-nitrimino-pyridine (IA), as was postulated by Tschitschibabin and Menschikow and proved by methylation with dimethyl sulphate in alkaline medium (1), or with diazomethane in ether solution (2). A similar tautomerism can be predicted for 4-nitraminopyridine (III and IIIA) (3). However, 3-nitraminopyridine (II) cannot assume



I IA IB IC

II IIB IIC

III IIIA IIIB IIIC

IV IVA IVB IVC

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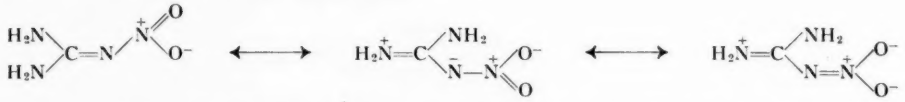
the nitrimine structure because the corresponding 3-pyridone structure is impossible (4). Also, 2-nitraminothiazole (IV) (5, 6) could exhibit a similar tautomerism to form the nitrimine (IVA).

The purpose of the present work was to study the infrared absorption spectra of the solid nitrimines of pyridine and thiazole series in order to establish the correlation between the structure and spectra. The results of the infrared study could give additional information on the structure of these substances in the crystal state. It is obvious that the structure of the solid nitrimines could differ from that established in solutions. It was expected beforehand that the presence of the heterocyclic ring in the nitrimines could greatly influence the positions of the absorption bands of the NH and NO_2 groups compared with the spectra of aliphatic nitramines. The anticipation was mainly based on facts established by several workers, that the change of a trivalent nitrogen atom to a substituted ammonium cation causes certain shifts in the infrared absorption bands (*vide infra*) (7, 8, 9, 10, 11, 12). A similar shift could be expected in the spectra of nitrimino- pyridines and -thiazoles. The nitrimino tautomeric forms IA to IVA possess resonance hybrid structures, as has been postulated by Taurins and Viron (2) for I and IA, and the most important resonance structures of the nitrimines could arise by the electron shift from the heterocyclic ring nitrogen to the nitrimino group creating a positive charge on the ring nitrogen atom. There are no resonance structures of the nitramino tautomeric form of I to IV having a positive charge on the pyridine ring nitrogen.

It is well established that resonance is present also in other compounds containing nitrimino groups and basic nitrogen atoms. On the basis of the study of electronic spectra McKay, Picard, and Brunet (13) concluded that nitroguanidine existed as a resonance hybrid of several contributing structures:



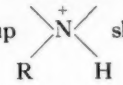
This was confirmed by Bryden, Burkardt, Hughes, and Danouhe (14) by the determination of the crystal structure of nitroguanidine. The equality of the three carbon–nitrogen distances (1.34–1.35 Å) indicated that the second structure contributes predominantly.

Resonance hybrid structures have also been considered for the anion of the monoacid salt of 5-nitraminotetrazole by Lieber, Sherman, and Pantikin (15).

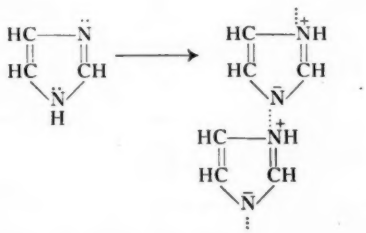
Some of the papers dealing with the shift of the infrared absorption bands are mentioned here briefly. It has been found that amines and their salts absorb differently in the infrared high-frequency region (7). Heacock and Marion (8) have investigated a number of secondary amines and their salts. They found that the spectra of the salts contain several absorption bands which are absent from the spectra of the amines. The new bands in the region 1620 to 1560 cm.$^{-1}$ are characteristic of secondary amine salts, and they arise by $\overset{+}{N}H_2$ deformation vibrations. In the spectra of tertiary amine salts, the stretching vibrations of the $\overset{+}{N}$—H group are displaced towards lower frequencies. Lord and Merrifield (9) have reported that in the spectrum of pyridine hydrochloride the $\overset{+}{N}$—H stretching band at 2450 cm.$^{-1}$ is broad and structureless and that this band is accompanied by absorption maxima at 1980 and 2090 cm.$^{-1}$.

α-Amino acids, which exist in the form of dipolar ions, do not exhibit any bands in the region 3400–3300 cm.$^{-1}$ (with the exception of isovalin) (10) which could be expected

if the amino group were free. Instead, a wide and structureless band occurs between 3030 and 2546 cm.$^{-1}$, which is given by C—H and $\overset{+}{N}H_3$ stretching vibrations. In most of the spectra of α-amino acids, there is also a band at 2128 cm.$^{-1}$ present which arises by the $-\overset{+}{N}H_3$ stretching vibrations only.

From the study of the infrared spectra of myosmine and nicotine, and their mono- and di-hydrochlorides, Witkop (11) showed that it is possible to distinguish the type of substituted nitrogen cations. The substituted ammonium group  showed the absorption at 2440–2350 cm.$^{-1}$, and the immonium group at 2095–1980 cm.$^{-1}$.

The absence of the infrared absorption at 3300 cm.$^{-1}$ by imidazole in the solid state and in concentrated solutions led Otting (12) to an explanation that, in imidazole, protons are transferred from the NH groups to the tertiary nitrogen atoms giving rise to positively and negatively charged nitrogen atoms which become associated by ionic charges:



In dilute chloroform solutions, the association of imidazole is broken and the spectrum shows a maximum at 3450 cm.$^{-1}$ characteristic of the free N—H group of imidazole.

EXPERIMENTAL

The infrared spectra of nitramines were recorded with a Perkin-Elmer Model 21 double beam spectrophotometer. The settings of the instrument were as follows: resolution 927, gain 5, speed 5, response 1, suppression 0. The spectrum of *n*-butylnitramine was taken in a 0.025 mm. NaCl cell. The solid nitramino-pyridines and -thiazoles were investigated in potassium bromide pellets. The substance (1 mg.) and potassium bromide (0.4 g.) were mixed and ground by vibrating in a 1 ml. glass-stoppered tube with four steel balls for 3 minutes in a Perkin-Elmer magnetic vibrator. The pellets were pressed in a Perkin-Elmer die for 2 minutes by applying a pressure of 20,000 lb./sq. in. *n*-Butylnitramine was prepared by Mr. C. C. Bombardieri; and 2-, 3-, and 4-nitriminopyridine, and 2-nitrimino- and 4-methyl- and 4,5-dimethyl-2-nitrimino-thiazoles were made by Mr. S. Kasman. The results have been summarized in Tables I, II, and III.

RESULTS AND DISCUSSION

Region 3800–2000 cm.$^{-1}$

The infrared spectrum of the liquid *n*-butylnitramine was compared with the spectra of 2-, 3-, and 4-nitriminopyridines and 2-nitriminothiazole in the region 3800–2000

TABLE I

POSITIONS OF ABSORPTION MAXIMA ($cm.^{-1}$) IN THE INFRARED SPECTRA OF NITRIMINO-(1H)PYRIDINIUM HYDROXIDES, INNER SALTS

Assignment	2-Nitrimino-	3-Nitrimino-	4-Nitrimino-
a. $\overset{+}{N}$—H stretching	3230vw	3175vw	
	3015w	3110vw	3020w
	2800m[1]	2620[2]	2620m[2]
	2260vw	2120m	
	2020vw		2035w
	1947vw		1940w
	1882vw		
b. Pyridine ring; sym. and asym. nitrimino stretching	1625vs	1630s	1628s
	1603vs	1598s	1607s
	1543vs	1543vs	1512m
	1478s	1467s	1457s
	1427vs		1442s
	1375s	1395vs	1390s
c. Nitrimino sym. stretching	1337s	1345vs	
	1310s	1326s	1288s
	1265	1277s	
d. Pyridine ring skeletal vibrations	1225	1235s	1225vs
	1152s	1155s	1180vs
	1137m		1160vs
	1112m	1115m	1095s
		1070w	
	1045w	1060w	
	1025w(sh)	1020vw	1038w
	1007m	1005w	1007w
e. Out-of-plane vibrations: (4) C—H, (5) nitrimino group	989[4]		
	940[5]		932[4]
		895(sh)[4]	
	880w[5]	877m[5]	885s[5]
		805s[4]	882s
	770vs[4]	770m	771m[4]
	727w[4]	752m	
	672m	670s[5]	656w[5]

[1] *Wide band at 2880–2700 cm.$^{-1}$.*
[2] *Wide band at 2880–2550 cm.$^{-1}$.*
[3] *Wide band at 2800–2550 cm.$^{-1}$.*
[4],[5] *See under e. above, first column.*

TABLE II

POSITIONS OF ABSORPTION MAXIMA ($cm.^{-1}$) IN THE INFRARED SPECTRA OF 2-NITRIMINO-(3H)THIAZOLIUM HYDROXIDES, INNER SALTS

Assignment	2-Nitrimino-	2-Nitrimino-4-methyl-	2-Nitrimino-4,5-dimethyl-
a. $\overset{+}{N}$—H stretching	3140ms	3140ms	3160(sh)
	3090		3110ms
	2985	3000w(sh)	3000m
	2920		
	2870		2880(sh)
			2765(sh)
	2270		
b. Nitrimino asym. stretching	1567vs	1600ms	1625s
c. Thiazole ring	1525vs	1530w(sh)	1545sh
		1515w	1535s
		1502w(sh)	
	1476vs	1465m(sh)	1485s

TABLE II (*Concluded*)

POSITIONS OF ABSORPTION MAXIMA (cm.$^{-1}$) IN THE INFRARED SPECTRA OF 2-NITRIMINO-(3H)THIAZOLIUM HYDROXIDES, INNER SALTS (*Concluded*)

Assignment	2-Nitrimino-	2-Nitrimino-4-methyl-	2-Nitrimino-4,5-dimethyl-
d. Methyl groups		1450vs 1435ms(sh)	1445m
e. Nitrimino sym. stretching and thiazole ring	1395s	1375m	1400m 1380w
	1320s	1310s	1315m
f. Nitrimino sym. stretching	1285vs	1295vs 1280s(sh)	1272vs
	1257vs	1265s	
	1247vs	1240vs	1240vs
g. Thiazole ring skeletal vibrations	1117s	1150s	
	1068w	1040w	1030vw
	1028w		
	1008vw	1000w	
h. C—H and nitrimino out-of-plane vibrations		960w	982vw
	883s		880w
	844s	840ms	
		815ms	820m
	793m		795w
	762m	765ms	765m
	723m		
	707vs		
		675w	685m
	627vw		

TABLE III

POSITIONS OF ABSORPTION MAXIMA (cm.$^{-1}$) IN THE INFRARED SPECTRUM OF *n*-BUTYLNITRAMINE

Assignment	*n*-Butylnitramine
a. N—H stretching	3300vs 3160s(infl.)
b. CH_3 and CH_2 stretching	2920vs 2880vs
c. Nitramino asym. stretching	1580vs* 1565s(sh)
d. CH_2 asym. bending	1460m* 1405m*
e. Nitramino sym. stretching	1325vs* 1270w 1235m 1155w 1120m
f. C—H out-of-plane vibrations	775w 745

**Wide, strong bands.*

cm.$^{-1}$. The inclusion of *n*-butylnitramine in the infrared study was essential in answering the question whether the shift of —N—H absorption bands in this region arises by the association of the —N—H group with oxygen of the nitro group, or by the resonance effect. Since there is no resonance between the *n*-butyl group and nitramino group in

n-butylnitramine, the association of the —N—H group could be the only determining factor in shifting the absorption band from 3300 cm.$^{-1}$ to lower frequencies. The examination of the spectrum of *n*-butylnitramine shows that the absorption band of the N—H bonds has not been shifted but occurs at the expected position of 3300 cm.$^{-1}$. Consequently, there is no association in the liquid *n*-butylnitramine to such extent that it could influence the absorption of —N—H groups.

The analysis of the infrared spectra of the solid 2-, 3-, and 4-nitriminopyridines indicates clearly that there are no absorption bands in the region 3400–3200 cm.$^{-1}$ which could arise if the N—H group was present either in the nitramino (I to III), or nitrimino (IA to IIIA) structures. Instead of these bands, the three nitriminopyridines give wide bands between 2880 and 2550 cm.$^{-1}$. 2-Nitriminothiazole shows only a wide band between 3140 and 2270 cm.$^{-1}$, thus excluding structures IV and IVA.

These data indicate that the structures of nitriminopyridines and 2-nitriminothiazoles do not correspond to the classical formulae I to IV and IA to IVA assigned by Tschitschibabin. Since there is a very small probability that the solid heterocyclic nitrimines are associated by —N—H groups, it must be concluded that the shift of the infrared absorption bands of pyridine and thiazole nitrimines arises from the structures formed by the resonance effect. The resonance in these compounds allows the formation of pyridinium and thiazolium betaines possessing a positively charged nitrogen of the heterocyclic rings, and a negative charge located on the nitrimino group (structures IB to IVB and IC to IVC). Although nitrimino-pyridines and -thiazoles can conveniently be described as hybrids of several contributing structures, including also the IA to IVA, the infrared spectroscopic evidence points out that the structures IB to IVB and IC to IVC predominate. Accordingly, we propose to name the nitrimines of pyridine and thiazole series *nitrimino-(1H)pyridinium and nitrimino-(3H) thiazolium hydroxides, betaines (or inner salts)*. For example, the substance previously called 2-nitraminopyridine must be named 2-nitrimino-(1H)pyridinium hydroxide, betaine; the substance previously described as 4,5-dimethyl-2-nitraminothiazole must be designated 4,5-dimethyl-2-nitrimino-(3H)-thiazolium hydroxide, betaine.

The physical properties of these compounds are in good agreement with their dipolar structure. Contrary to aliphatic nitramines, which retain their old names, the heterocyclic nitrimino-(1H)pyridinium and -(3H)thiazolium hydroxides, betaines are only weakly acidic. They are insoluble in non-polar organic solvents and they possess relatively high decomposition points, without melting.

Region 1650–1235 cm.$^{-1}$, n-Butylnitramine

The infrared spectrum of *n*-butylnitramine has a very strong band at 1580 cm.$^{-1}$ which is given by the asymmetric vibrations of the nitro group. The symmetric stretching vibrations of this group produce a strong wide band at 1325 cm.$^{-1}$ accompanied by weaker bands at 1270 and 1235 cm.$^{-1}$. A band of high intensity at 1406 cm.$^{-1}$ arises by merging the absorption bands of the nitro and the methyl groups with the result of widening and intensifying of the band. There is no doubt that electronically the nitro group in *n*-butylnitramine is very similar to the nitro group in ordinary nitro compounds and therefore exhibits almost the same absorption maxima (16).

Region 1650–1375 cm.$^{-1}$, Nitrimino-(1H)pyridinium Betaines

In each of the infrared spectra of the three isomer monoaminopyridines (17), the first band in the region 1636 to 1400 cm.$^{-1}$ is shifted as much as 10 to 20 cm.$^{-1}$ towards lower frequencies, compared with the spectrum of liquid pyridine (18) which gives bands at

1636, 1584, 1485, and 1439 cm.$^{-1}$. The shift is even greater in the spectra of methylpyridines (18), the absorption beginning in the region 1604–1590 cm.$^{-1}$. Nitrimino-(1H)pyridinium betaines absorb at 1630 cm.$^{-1}$ and this band is followed by a number of peaks of high intensity in the region 1630–1375 cm.$^{-1}$ (Table I). It is obvious that the stretching vibrations of the double bonds of the pyridine ring and nitrimino group are close to each other and the final effect is the increasing of the band intensities. The nitrimino group shows its greatest effect on the bands at 1512–1543 cm.$^{-1}$ and 1478–1375 cm.$^{-1}$. It is also possible that the absorption frequency of the $\overset{+}{N}$—H group coincides with that of the pyridine ring at 1620 cm.$^{-1}$. Therefore, a very precise assignment of the band frequency to the nitrimino group is rather difficult.

Region 1000–650 cm.$^{-1}$, Nitrimino-(1H)pyridinium Betaines

In the spectra of the 2-, 3-, and 4-nitrimino-(1H)pyridinium betaines, there are bands at 672, 670, and 650 cm.$^{-1}$ respectively, which are absent in the spectra of pyridine, 2-, 3-, and 4-methylpyridines (18), and 2-aminopyridine (17). Therefore, these three bands must be considered as characteristic to the nitrimino group and can be assigned to the out-of-plane vibrations of this group. With the same type of vibrations probably are associated the strong bands at 880, 877, and 885 cm.$^{-1}$ occurring in the spectra of the three nitrimino-(1H)pyridinium betaines (Table I). This assignment is based on the observation that these bands are absent in the spectra of 2-amino- (17), 2-amino-3-methyl- (19), and 2-amino-5-methyl-pyridines (19) and they are weak in pyridine and in the three methylpyridines.

2-Nitrimino- and 4-nitrimino-(1H)pyridinium betaines possess characteristic bands at 940 and 932 cm.$^{-1}$ respectively, which are absent in the spectra of 2-, 3-, and 4-methyl-(18), 2-amino- (17), 2-amino-3-methyl- and 2-amino-5-methyl-pyridines (19).

Region 1650–1250 cm.$^{-1}$, 2-Nitrimino-(3H)thiazolium Betaines

The infrared spectrum of thiazole (20) possesses six strong absorption maxima between 1615 and 1200 cm.$^{-1}$, and in the spectrum of 2-nitrimino-(3H)thiazolium betaine there are eight bands (Table II) which are wider and more intense than the bands given by thiazole in the same region. The band at 1525 cm.$^{-1}$ exhibited by 2-nitrimino-(3H)-thiazolium betaine is characteristic of the ring vibrations of substituted thiazoles; for example, methylthiazoles (20) show absorption between 1505 and 1530 cm.$^{-1}$, and 2-aminothiazole (21) has a band at 1520 cm.$^{-1}$. The intense band at 1567 cm.$^{-1}$ given by nitrimino-(3H)thiazolium betaine must be assigned to the nitrimino group because it is wide and intense. The nitro groups of C-nitro compounds and of the nitramino group in *n*-butylnitramine absorb at the same frequency.

The skeletal vibrations of the substituted thiazole ring give bands also in the region 1210–1240 cm.$^{-1}$ and 1290–1340 cm.$^{-1}$. In the spectrum of 2-nitrimino-(3H)thiazolium betaine the corresponding bands of the thiazole ring are at 1247 cm.$^{-1}$. Some other bands at 1257, 1285, and 1320 cm.$^{-1}$ originate by the vibrations of the nitrimino group and thiazole ring. They are wide and of high intensity, similarly to the bands observed in the pyridine series.

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LYCOPODIUM ALKALOIDS

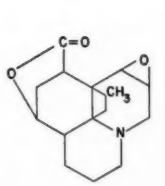
VI. REACTIONS OF THE DIPHENYL DERIVATIVE OF DESOXODIHYDROANNOTININE[1]

E. E. BETTS[2] AND DAVID B. MACLEAN

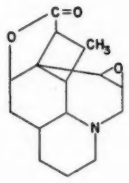
ABSTRACT

Desoxodihydroannotinine reacted with phenyl lithium to yield a diphenyl derivative, $C_{28}H_{35}O_2N$ (III). This compound yielded a ketone, $C_{28}H_{33}O_2N$ (V), upon oxidation by the Oppenauer procedure and a dihydroxyketone, $C_{28}H_{33}O_3N$ (VI), upon oxidation with chromic acid. A ketone VIII, epimeric with V, was obtained by treatment of III with potassium tertiary butoxide in cyclohexanone. Both V and VIII underwent elimination of their diphenyl carbinol groups upon treatment with potassium tertiary butoxide to yield an unsaturated ketone, $C_{15}H_{21}ON$ (IX), and benzohydrol. These reactions are discussed in relation to the recently proposed structures for the parent alkaloid, annotinine.

Annotinine, $C_{16}H_{21}O_3N$, the major alkaloid of *Lycopodium annotinum*, was first isolated by Manske and Marion (1). In a later paper they established the presence of a lactone ring and an ether ring in the molecule (2). The size of the ether ring and its relationship to the nitrogen atom were demonstrated by MacLean and Prime (3) while Wiesner *et al.* were able to relate the lactone ring to the other functions in the molecule (4). Several total structures for the alkaloid have been proposed in the past by Wiesner *et al.* (4, 5, 6) on the basis of dehydrogenation experiments on annotinine and its derivatives. In their latest publication (7) they have established the detailed structure of ring B (formula A) and have suggested that formula A adequately explains the reactions of annotinine.



A



B

Martin-Smith, Greenhalgh, and Marion (8) have also proposed a structure for annotinine which is represented in formula B. Arguments were advanced that their structure explained the dehydrogenation reactions of annotinine equally as well as previous structures of Wiesner's. However, the seven-membered nature of ring A is not consistent with the work of Betts and MacLean (9). Nor is the structure of ring B consistent with the latest work of Wiesner *et al.* (7), nor with the results of the present study.*

Annotinine (I) was converted to desoxodihydroannotinine† (II) by the method of Manske and Marion (2). This compound has the same ring structure as annotinine but lacks the epoxide function (9). It reacted readily with phenyl lithium to yield diphenyldesoxodihydroannotinine, $C_{28}H_{35}O_2N$ (III). This compound dehydrated readily with

[1]*Manuscript received September 12, 1957.*
Contribution from the Burke Chemical Laboratories, Hamilton College, McMaster University, Hamilton, Ontario.

[2]*Holder of a National Research Council Studentship, 1956–57.*

Formula B has since been withdrawn by Marion and Przybylska (Can. J. Chem.* **35, *1075 (1957)), who have shown by an X-ray investigation that annotinine has structure A.*

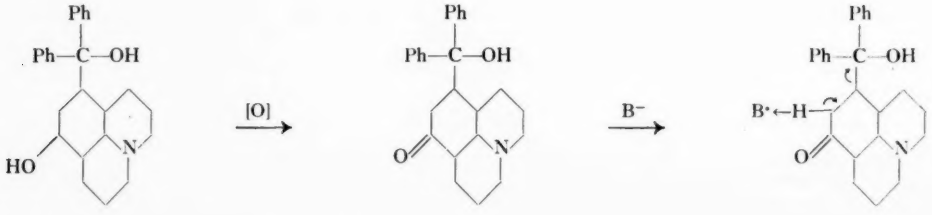
†*This compound has been previously called saturated lactone A, but the present name seems more descriptive and less ambiguous in the present context.*

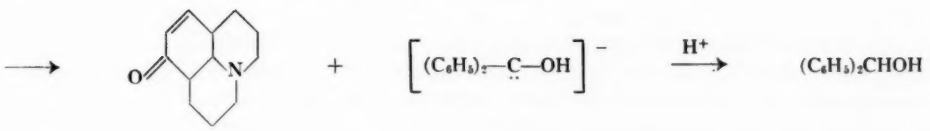
boiling, aqueous hydrochloric acid to yield the anhydro derivative, $C_{28}H_{33}ON$ (IV), which has an ultraviolet spectrum characteristic of a 1,1-diphenylethylene despite the fact that the compound would not absorb hydrogen at low pressures nor oxidize with ease. Oxidation of III with aluminum isopropoxide in the presence of cyclohexanone yielded the hydroxyketone, $C_{28}H_{33}O_2N$ (V), while oxidation with chromic acid in acetic acid yielded a dihydroxyketone, $C_{28}H_{33}O_3N$ (VI), also obtainable by the chromic acid oxidation of V. The new hydroxyl function in VI is probably tertiary in character; otherwise it would have been expected to oxidize in the medium. The activated positions in the molecule at which an hydroxyl group could be introduced are alpha to the carbonyl function to yield an α-hydroxyketone, or alpha to the nitrogen to yield a carbinolamine. Tests for a carbinolamine function were negative. Anhydronium salts of VI were not formed, the methiodide of VI was normal in character, and hydride reduction of VI or its hydrochloride yielded a trihydroxy compound, $C_{28}H_{35}O_3N$ (VII). Neither VI nor VII reacted with periodic acid, but VI reacted with lead tetraacetate with consumption of 3 moles of the reagent. The products of this reaction have not yet been characterized but are presently under study. The tetraacetate reaction, because of its complexity, cannot be considered evidence for an α-hydroxyketone structure in VI. However, the carbonyl absorption in the infrared of V and VI lies at 1700 cm.$^{-1}$ and 1720 cm.$^{-1}$, respectively. This shift implies a close structural relationship between the two groups in which the hydroxyl function is alpha and axial to the carbonyl function. Furthermore it has been shown in a similar series of reactions on diphenylannotinine (10) that the introduction of the new hydroxyl function is dependent on the presence of the carbonyl group. The evidence, therefore, points to an α-hydroxyketone structure for VI.

We also examined the oxidation of III with potassium tertiary butoxide and cyclohexanone. When this reaction was carried out in refluxing benzene, a ketone, $C_{28}H_{33}O_2N$ (VIII), was isolated; in refluxing toluene the reaction proceeded to yield a conjugated ketone, $C_{15}H_{21}ON$ (IX), identified through its hydrochloride and hydrobromide salts. Both V and VIII were also converted to IX by treatment with potassium tertiary butoxide in refluxing toluene.

The formation of IX directly from III or from V or VIII requires the elimination of the diphenyl carbinol group and it has been shown that it was eliminated as benzohydrol. When V was heated with potassium tertiary butoxide in an atmosphere of oxygen-free nitrogen, a quantitative recovery of benzohydrol was realized. In the presence of air some of the benzohydrol was converted to benzophenone, which was isolated as its 2,4-dinitrophenylhydrazone. In the reaction of III with potassium tertiary butoxide and cyclohexanone the presence of benzophenone was indicated in the non-basic fraction through its carbonyl absorption in the infrared at 1660 cm.$^{-1}$.

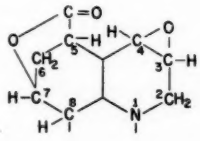
This reaction is very likely a reverse Michael reaction and can be depicted according to the sequence below:





The formation of ketone VIII in the presence of potassium tertiary butoxide and ketone V in the presence of aluminum isopropoxide might suggest a more deep-seated difference between the two isomers than that of simple epimers. However, ketone V was partially converted into ketone VIII by prolonged refluxing with sodium ethoxide, a reagent which would not be expected to bring about other changes in the system. The more rapid transformation induced by potassium tertiary butoxide is likely related to its greater basic strength and greater ionic character. The two ketones V and VIII behave differently toward chromic acid in glacial acetic acid. It was pointed out previously that V was readily converted to VI by this oxidant. However, VIII was recovered unchanged upon similar treatment. This difference in behavior toward chromic acid is probably dependent on the conformation of the tertiary hydrogen in the two compounds.

The ultraviolet spectrum of IX has a peak at 2280 Å, log $\epsilon = 3.85$, which is characteristic of an α,β-unsaturated ketone with a single β-alkyl substituent (11). Thus, position "6" (formula A) must be a methylene group. The isomeric ketones V and VIII can be epimeric only at position "8" while compound VI will carry its hydroxyl function at the same position. The detailed structure of annotinine can therefore be extended to that represented by the partial formula below, which is in complete accord with the recent work of Wiesner *et al.* (7).



EXPERIMENTAL

Diphenyldesoxodihydroannotinine

A solution of phenyl lithium in 150 ml. ether was prepared from 4 g. of lithium and 40 g. of bromobenzene and treated with 6 g. of desoxodihydroannotinine (prepared from annotinine by the method of Manske and Marion (2)) dissolved in 100 ml. of ether. After addition was complete the mixture was refluxed for 2 hours, cooled, and decomposed in ice – hydrochloric acid. Some insoluble hydrochloride separated at this point. The ether layer was separated and washed with dilute hydrochloric acid. The acid washings and original aqueous portion were combined, made alkaline with ammonia, and extracted four times with ether. The ether extracts were dried and concentrated to yield a residue which deposited 3.5 g. of crystalline product from an acetone solution. The mother liquors were treated with concentrated hydrochloric acid to yield a crystalline hydrochloride. The total recovery as base and as hydrochloride represented a yield of 75–80%.

The base was recrystallized from acetone to yield a product which melted at 218°–220° C. Calc. for $C_{28}H_{35}O_2N$: C, 80.57; H, 8.39%. Found: C, 80.39, 80.65; H, 8.75, 8.81%.

The ultraviolet spectrum in ethanol had λ_{max} 2580 Å, log $\epsilon = 2.8$. The infrared spectrum showed hydroxyl absorption at 3600 cm.$^{-1}$ and 3150 cm.$^{-1}$ (broad) and weak phenyl absorption at 1590 cm.$^{-1}$. $[\alpha]_D^{21} = -106°$ (c, 1% in chloroform).

Dehydration of Diphenyldesoxodihydroannotinine

A solution of 0.150 g. of diphenyldesoxodihydroannotinine in 2.5 ml. of concentrated hydrochloric acid and 7.5 ml. of methanol was refluxed for 2 hours, and then evaporated to dryness. Addition of acetone yielded a crystalline hydrochloride which after recrystallization from methanol–acetone melted at 295° C. with decomposition. Calc. for $C_{28}H_{33}ON.HCl$: C, 77.15; H, 7.83; N, 3.21%. Found: C, 76.45, 76.41; H, 8.21, 7.76; N, 3.13, 3.26%.

The hydrochloride was converted to the free base by suspension in aqueous ammonia and extraction with ether. The dried ether extracts yielded a residue on evaporation, which after recrystallization from methanol melted at 189°–190° C. Calc. for $C_{28}H_{33}ON$: C, 84.21; H, 8.27; N, 3.50%. Found: C, 83.67, 83.84; H, 8.59, 8.61; N, 3.70%.

The infrared spectrum (chloroform) had hydroxyl absorption at 3630 cm.$^{-1}$ and phenyl absorption at 1600 cm.$^{-1}$ and conjugated phenyl at 1580 cm.$^{-1}$. The ultraviolet absorption spectrum had strong but broad absorption in the region 2200–2800 Å, $\log \epsilon = 3.6$–4.0. No definite band was detectable.

When this base was treated with hydrogen at 50 p.s.i.g. for 12 hours over Adam's catalyst, it failed to take up hydrogen and was recovered unchanged. It was also resistant to the action of potassium permanganate in acetone.

Oxidation of Diphenyldesoxodihydroannotinine with Aluminum Isopropoxide and Cyclohexanone

A solution of 1.2 g. of aluminum isopropoxide in 30 cc. of dry toluene was treated with 0.5 g. of compound III and 1.5 cc. of cyclohexanone. The reaction mixture was refluxed 1 hour and 15 minutes, cooled and poured on ice. The toluene layer was separated and the aqueous layer was further extracted three times with ether. The toluene and ether extracts were combined and washed four times with 10% hydrochloric acid. The acid washings were made alkaline with ammonium hydroxide and extracted with ether. The ether extracts were dried with anhydrous sodium sulphate and taken to dryness. The residue crystallized on addition of ether. The product (0.350 g.), after two recrystallizations from ether, melted sharply at 201° C. A mixed melting point with the ketone isolated from the oxidation using potassium tertiary butoxide was depressed 10°. Calc. for $C_{28}H_{33}O_2N$: C, 80.97; H, 7.95; N, 3.37%. Found: C, 80.98, 81.08; H, 7.74, 7.73; N, 3.25%.

The infrared spectrum (nujol) had phenyl absorption at 1595 cm.$^{-1}$, carbonyl absorption at 1700 cm.$^{-1}$, and a band in the hydroxyl region at 3500 cm.$^{-1}$. $[\alpha]_D^{21} = +100.7$ (*c*, 1% in chloroform).

Chromic Acid Oxidation of $C_{28}H_{33}O_2N$ (*V*)

A sample of compound V (0.108 g.) was dissolved in 5 cc. glacial acetic acid, the solution was warmed to 50°–60°, and excess CrO_3 in water added. After 10 minutes the excess CrO_3 was destroyed with methanol and the resulting green solution was taken to dryness under reduced pressure. Water was added to the residue, the mixture was made alkaline with ammonium hydroxide and extracted four times with ether. The combined ether extracts were dried with sodium sulphate and the ether removed. The residue (0.086 g.) was taken up in methanol and acidified with hydrochloric acid. The hydrochloride of the reaction product, after recrystallization from methanol, melted at 273°. A mixed melting point with the hydrochloride of VI was not depressed. (Yield, 50%.) The infrared spectrum was similar to that of compound VI described below.

Oxidation of Diphenyldesoxodihydroannotinine with Chromic Acid

A solution of 1.0 g. of compound III in 20 ml. of glacial acetic acid was warmed to 50°–60° and treated with concentrated aqueous solution of chromic acid in water until the dichromate color was persistent. The excess oxidizing agent was destroyed with methanol and the solution was taken to dryness under reduced pressure. The residue was taken up in water, made basic with ammonia, and exhaustively extracted with ether. The ether extracts were dried and evaporated. The residue was taken up in methanol and acidified with hydrochloric acid, whereupon the hydrochloride separated in crystalline form. Recrystallization from methanol yielded a compound which melted at 276° C. Calc. for $C_{28}H_{33}O_3N.HCl.H_2O$: C, 69.20; H, 7.48; N, 2.88%. Found: C, 69.11, 69.10; H, 7.74, 7.84; N, 2.98, 2.86%.

The infrared spectrum (nujol) had absorption at 1595 cm.$^{-1}$ (phenyl), 1720 cm.$^{-1}$ (carbonyl), and broad absorption in the region 3350–3420 cm.$^{-1}$. The ultraviolet spectrum had λ_{max} at 2600 Å, log ϵ = 2.69.

The base was regenerated from the hydrochloride by treatment with aqueous ammonia and extraction with ether. It was recrystallized from methanol to yield a product which melted at 208° C. Calc. for $C_{28}H_{33}O_3N$: C, 77.94; H, 7.65; N, 3.25; act. H (2), 0.46%. Found: C, 77.94, 78.09; H, 7.81, 7.77; N, 3.65; act. H, 0.47, 0.53%.

The infrared spectrum (nujol) showed phenyl absorption at 1590 cm.$^{-1}$, carbonyl absorption at 1720 cm.$^{-1}$ (shoulder at 1728 cm.$^{-1}$), and hydroxyl absorption at 3450 cm.$^{-1}$ and 3500–3550 cm.$^{-1}$. The ultraviolet spectrum had λ_{max} at 2600 Å, log ϵ = 2.9. $[\alpha]_D^{21}$ = +43.0 (*c*, 1% in chloroform).

Compound VI (0.20 g.) was treated with 3 ml. of methyl iodide and the mixture allowed to stand at room temperature for 2 days. The crystalline solid which had separated (0.05 g.) was recrystallized from acetone and melted at 245° C. Calc. for $C_{28}H_{33}O_3N.CH_3I$: C, 60.71; H, 6.32; N, 2.44%. Found: C, 60.80, 60.67; H, 6.62, 6.38; N, 2.91%.

The infrared spectrum had phenyl absorption at 1600 cm.$^{-1}$, carbonyl absorption at 1720 cm.$^{-1}$, and a double peak in the hydroxyl region at 3250 cm.$^{-1}$ and 3430 cm.$^{-1}$.

Reduction of $C_{28}H_{33}O_3N$ *(VI) with Lithium Aluminum Hydride*

A solution of 0.4 g. of $C_{28}H_{33}O_3N$ in 40 ml. of anhydrous ether was added slowly to a solution of 1.0 g. of lithium aluminum hydride in 30 ml. of anhydrous ether. The reduction mixture was refluxed for 2.5 hours when the excess hydride was destroyed with wet ether followed by addition of a few milliliters of water. The ether solution was separated and evaporated to dryness to yield 0.34 g. of residue. The residue was dissolved in acetone and acidified with hydrochloric acid. The crystalline hydrochloride, obtained upon evaporation of the acetone, was recrystallized twice from methanol (m.p. 272° C.). The base was regenerated from the hydrochloride by extraction with ether from an aqueous ammoniacal solution. It was recrystallized twice from ether and melted at 209°. Calc. for $C_{28}H_{35}O_3N$: C, 77.56; H, 8.13%. Found: C, 77.71, 77.59; H, 8.14, 8.18%.

The infrared spectrum showed absorption at 1595 cm.$^{-1}$ (phenyl) and at 3620 cm.$^{-1}$ (slight) and 3430 cm.$^{-1}$ (broad) in the hydroxyl region.

Treatment of the hydrochloride of VI by the same procedure yielded the same product.

Reaction of $C_{28}H_{33}O_3N$ *(VI) with Lead Tetraacetate*

Compound VI (179 mg.), dissolved in 40 ml. of glacial acetic acid, was added to a mixture of 50 ml. of 0.1 *N* lead tetraacetate in glacial acetic acid. To this mixture 5 ml.

of water was added and the volume was made up to 100 ml. by the addition of glacial acetic acid. A blank was prepared in the same manner omitting only the sample. Aliquots of 10 ml. were withdrawn at intervals, added to 15 ml. of buffer solution containing 5 g. potassium iodide and 125 g. of potassium acetate in 250 ml. of solution. The liberated iodine was titrated with 0.02 *N* sodium thiosulphate. After about 30 hours 3 moles of reagent per mole of compound VI had been consumed, whereupon the reaction virtually ceased.

Oxidation of Diphenyldesoxodihydroannotinine with Cyclohexanone and Potassium Tertiary Butoxide

A solution of 0.2 g. of III in 20 ml. of toluene was treated with 1 ml. of cyclohexanone and 0.28 g. of freshly prepared potassium tertiary butoxide for 1 hour under reflux. The mixture was decomposed in ice water, the toluene layer separated, and the aqueous layer extracted three times with ether. The toluene and ether extracts were combined and extracted several times with 10% hydrochloric acid. The acid washings were made alkaline with ammonia and extracted with ether. The dried ether extracts yielded 0.1 g. of basic material which was dissolved in acetone and treated with concentrated hydrochloric acid. A crystalline hydrochloride separated, which after recrystallization from acetone melted at 261°–262° C. Calc. for $C_{15}H_{21}ON.HCl$: C, 67.26; H, 8.28; N, 5.27%. Found: C, 67.61, 67.62; H, 8.49, 8.77; N, 5.80, 5.80%.

The hydrobromide was prepared by a similar procedure and recrystallized from acetone–methanol. It melted at 267°–268° C. Calc. for $C_{15}H_{21}ON.HBr$: C, 57.68; H, 7.10%. Found: C, 57.54, 57.54; H, 6.89, 6.90%.

The ultraviolet spectrum of the hydrochloride showed weak absorption at 3180 Å (carbonyl) and had maximum absorption at 2280 Å, $\log \epsilon = 3.85$ (conjugated carbonyl). The infrared spectrum had peaks at 1680 cm.$^{-1}$ (conjugated carbonyl) and 1625 cm.$^{-1}$ unsaturation.

The ether–toluene mixture was examined for non-basic material. Evaporation yielded an oily residue which was mostly cyclohexanone. Examination of the infrared spectrum revealed the presence of a strong carbonyl band at 1660 cm.$^{-1}$, which corresponded to that of benzophenone, as well as the cyclohexanone carbonyl absorption at 1710 cm.$^{-1}$.

In another experiment carried out in refluxing benzene for 15 minutes, only a trace of conjugated ketone was obtained. There was isolated instead another compound which crystallized from ether and melted at 223° C. (Yield, 25%.) Calc. for $C_{28}H_{33}O_2N$: C, 80.93; H, 8.00; N, 3.30%. Found: C, 80.83, 80.67; H, 8.02, 8.03; N, 3.12%.

The infrared spectrum of this material had absorption at 1595 cm.$^{-1}$ (phenyl), 1710 cm.$^{-1}$ (carbonyl), and 3420 cm.$^{-1}$ (hydroxyl). The ultraviolet spectrum was similar to that of the starting material, $\lambda_{max} = 2580$ Å, $\log \epsilon = 2.75$. $[\alpha]_D^{21} = -60.2°$ (*c*, 1% in chloroform).

The mother liquors remaining after the separation of the above compound yielded a residue which melted over a wide range and was probably a mixture of V and VIII.

Treatment of $C_{28}H_{33}O_2N$ (*V*) *with Potassium Tertiary Butoxide in Toluene*

Compound V (0.33 g.) was dissolved in 30 ml. of dry toluene, 0.45 g. of freshly prepared potassium tertiary butoxide was added, and the mixture was refluxed for 30 minutes under an atmosphere of oxygen-free nitrogen. The reaction mixture was worked up for recovery of the conjugated ketone as described in the previous experiment. The non-basic material remaining in the toluene–ether layer was recovered by evaporation of the solvent under vacuum. The residue (0.148 g.) had an infrared spectrum identical

to authentic benzohydrol. It was recrystallized from petroleum ether and melted at 70° C. either alone or in admixture with an authentic sample of benzohydrol.

The basic material yielded a hydrochloride identical to the hydrochloride of the conjugated ketone.

When the reaction was carried out in air rather than nitrogen, the non-basic fraction was a mixture of benzohydrol and benzophenone. The latter was identified by conversion to its 2,4-dinitrophenylhydrazone.

Attempted Oxidation of VIII with Chromic Acid in Acetic Acid

About 40 mg. of VIII was dissolved in acetic acid and treated with a solution of CrO_3 in H_2O at 50°–60° for 10 minutes. After the excess CrO_3 was destroyed with methanol, the solution was taken to dryness under reduced pressure. The residue was taken up in water, the mixture was made alkaline and extracted with ether. Concentration of the dried ether extracts yielded the starting material.

Treatment of V with Sodium Ethoxide

Compound V (0.13 g.) was refluxed overnight in a dilute solution of sodium ethoxide in ethanol. The solution was evaporated to dryness, water was added, and the mixture was extracted with ether. The dried ether extracts were concentrated and seeded with a crystal of compound VIII. After 2 hours the crystalline needles (20 mg.) were separated from the solution by filtration. They melted at 220° C. and did not depress the melting point of VIII. The residual material obtained from the mother liquors melted over a wide range and was likely a mixture of V and VIII.

ACKNOWLEDGMENTS

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D-APIOSE[1]

P. A. J. GORIN AND A. S. PERLIN

ABSTRACT

Naturally-occurring apiose is shown by synthesis to be the D-isomer in the open-chain form. In this synthesis 3-*O*-benzyl-D-fructose is cyanohydrated and the resulting heptonic lactones are reduced to 3-*O*-benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol. The latter is oxidized with lead tetraacetate affording 2-*O*-benzyl-3-*C*-(hydroxymethyl)-D-*glycero*-tetrose which, on debenzylation, gives 3-*C*-(hydroxymethyl)-D-*glycero*-tetrose (D-apiose).

INTRODUCTION

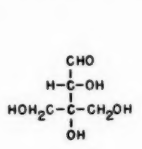
Apiose was first isolated by Vongerichten (1), who recognized it as a component sugar of the parsley flavone glycoside, apiin. The sugar has since been found in still other glycosides present in parsley (2, 3, 4, 5) and more recently in *Posidonia australis* (6) and in the rubber plant, *Hevea brasiliensis* (7). The researches of Vongerichten and later work by Schmidt (8), which have been reviewed by Hudson (9), established that apiose is a branched-chain pentose whose structure is represented by I. The synthesis of DL-apiose (10) provides additional confirmation of this structure. In the open-chain form the compound possesses only one asymmetric center, at carbon atom 2, for which the D-configuration has been assigned (8) by application of the salt–acid (11, 12) and phenylhydrazide and amide (12, 13) rules to the derived apionic acid and its derivatives. The present study furnishes an alternative proof for the configuration at C-2 through synthesis of D-apiose, which is found to be identical with the naturally-occurring sugar.

A ready synthetic pathway to D-apiose was suggested by the preparation of 4-*C*-(hydroxymethyl)-D-*threo*-pentose[2] (II) by Woods and Neish (14). It was apparent that D-apiose could be obtained by a one-step descent of the sugar series. However, attempts to achieve this by the Weerman degradation (15) or by partial lead tetraacetate oxidation (16) resulted in the production of only trace amounts of the desired product.

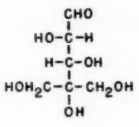
An alternative synthetic pathway, starting with 3-*O*-benzyl-D-fructose (III), was more successful. 1,2;4,5-Di-*O*-*iso*propylidene-D-fructose (17) was benzylated to give 3-*O*-benzyl-1,2;4,5-di-*O*-*iso*propylidene-D-fructose. The acetone groups were removed by acid hydrolysis, affording sirupy 3-*O*-benzyl-D-fructose (III), which was characterized by formation of 3-*O*-benzyl-D-glucose phenylosazone (18) on treatment with phenylhydrazine acetate. The 3-*O*-benzyl-D-fructose was cyanohydrated, the nitrile was hydrolyzed under alkaline conditions, and the product was acidified, yielding a mixture of the corresponding *O*-benzyl-α- and -β-D-fructoheptonic lactones (e.g., IV); the β-isomer was isolated as the crystalline γ-lactone. Reduction of the mixture with sodium borohydride (19, 20) gave the sirupy alcohol, 3-*O*-benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol (V). The structure of V was confirmed by its conversion, on catalytic hydrogenolysis with palladium oxide followed by acetylation, to the known hepta-*O*-acetyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol ("D-fructoheptitol" heptaacetate (21)).

[1]*Manuscript received November 17, 1957.*
Contribution from the National Research Council of Canada, Prairie Regional Laboratory, Saskatoon, Saskatchewan.
Issued as N.R.C. No. 4612 and Paper No. 250 on the Uses of Plant Products.
Presented at the 40th Annual Conference of the Chemical Institute of Canada, Vancouver, B.C., June 3–5, 1957.
[2]*The nomenclature of the branched-chain sugar has recently been discussed by F. Shafizadeh, Advances in carbohydrate chemistry,* ***11****, 263 (1956).*

The alcohol (V) rapidly consumed approximately 2 moles of oxidant when treated with lead tetraacetate in acetic acid or aqueous periodate, but a moderately rapid over-oxidation followed, which was more pronounced with the latter reagent. Consumption of 2 moles of oxidant was expected to correspond to cleavage of the 1,2,3-triol of V affording 2-*O*-benzyl-3-*C*-(hydroxymethyl)-D-*glycero*-tetrose (2-*O*-benzyl-D-apiose) (VI), in preference to attack at the tertiary hydroxyl group (22). Accordingly, V was oxidized



(I)



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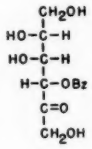

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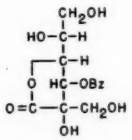

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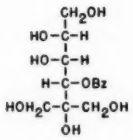
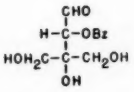


(V)



(VI)

with 2 moles of lead tetraacetate in acetic acid and the product was treated with methanolic hydrogen chloride to promote formation of the methyl glycosides. The latter were debenzylated with hydrogen – palladium oxide and the product hydrolyzed with aqueous acid. The final material was found by paper chromatography to contain three components present in approximately equal proportions, the central component corresponding in its rate of travel to D-apiose (I). Presence of the faster- and slower-moving components suggests that over- and under-oxidation occur in addition to the desired reaction on treatment of IV with lead tetraacetate.

The product corresponding to D-apiose was separated as a sirup from the mixture by column chromatography on cellulose (23). Its rate of travel on a paper chromatogram was identical with that of authentic D-apiose isolated from parsley. Detected on the chromatogram with the aniline oxalate spray (24) the natural and synthetic sugars each gave a faint yellow-brown spot which exhibited a strong yellow fluorescence under ultraviolet light, a characteristic of tetroses (25). The identity of the two compounds was demonstrated further by the fact that they gave identical infrared absorption spectra and 2,5-dichlorophenylosazones (6). The specific rotation of the synthetic specimen was $[\alpha]_D$ +6.4°, which is in good agreement with the values of $[\alpha]_D$ +3.8° found by Vongerichten and Müller (26) and $[\alpha]_D$ +5.8° found by Schmidt (8) for D-apiose obtained by regeneration from the 1-benzyl-1-phenylhydrazone.

Since the configuration of carbon atom 2 of synthetic D-apiose, originally carbon atom 3 of D-fructose, is known, the present results confirm Schmidt's assignment of the D-configuration to naturally-occurring apiose.

EXPERIMENTAL

Paper chromatography was carried out on Whatman No. 1 paper using *n*-butanol–ethanol–water (40: 11: 19, v/v) as solvent. Chromatograms were developed with aniline

oxalate (24) and ammoniacal silver nitrate (27) sprays. The distance travelled by compounds on chromatograms (R_{Rh}) was measured relative to the distance travelled by L-rhamnose. Evaporations were carried out *in vacuo* at 40° C.

3-O-Benzyl-1,2;4,5-di-O-isopropylidene-D-fructose

1,2;4,5-Di-*O-iso*propylidene-D-fructose (17) (45 g.) was dissolved in a mixture of benzyl chloride (75 ml.) and xylene (50 ml.). The solution was agitated vigorously with an Ultra-Turrax stirrer (28) and powdered potassium hydroxide (180 g.) was added during a period of 0.5 hour, the reaction temperature being maintained at 85°–95° C. during this time and for an additional 1.5 hours' reaction period. The mixture was cooled, washed with water three times, and concentrated. Water was added to the resulting sirup and the suspension heated on the steam bath at 1 mm., more water was added, and the evaporation repeated. The residue was taken up in acetone, filtered through a bed of filter-cel, and concentrated, yielding a yellow, viscous sirup; n_D^{24} 1.5080. Weight 59.0 g. After distillation (135°–155° C. at 0.05 mm.) the product was colorless and had n_D^{24} 1.5033, $[\alpha]_D^{25}$ −95.0° (*c*, 4.6, ethanol). Calculated for $C_{19}H_{26}O_6$: C, 65.12%; H, 7.48%. Found: C, 65.00%; H, 7.43%.

3-O-Benzyl-D-fructose

3-*O*-Benzyl-1,2;4,5-di-*O-iso*propylidene-D-fructose (55 g.), dissolved in 50% acetic acid (200 ml.), was heated on a steam bath for 18 hours. After evaporation of the solvent, the product was found (infrared absorption) still to contain some *iso*propylidene groups and was therefore treated on a steam bath for 2 hours with 0.1 *N* sulphuric acid. The hydrolyzate was neutralized with barium carbonate and the solution filtered and concentrated, affording a pale yellow amorphous solid $[\alpha]_D^{25}$ −24.9° (*c*, 4.1, water). Weight 30.4 g. On a paper chromatogram the product gave a single spot (R_{Rh} 2.4) detected by silver nitrate. Calculated for $C_{13}H_{18}O_6$: C, 57.77%; H, 6.71%. Found: C, 57.78%; H, 6.81%.

As expected for a 3-substituted ketose, the compound consumed lead tetraacetate slowly (29).

3-O-Benzyl-D-fructose-(D-glucose)-phenylosazone

3-*O*-Benzyl-D-fructose (400 mg.) was dissolved in water (10 ml.) containing acetic acid (1.5 ml.) and phenylhydrazine (1 ml.). The solution was kept at 50° C. for 18 hours and the red-brown mass which formed was taken up in methanol. On addition of water, crystals were deposited and these were recrystallized from aqueous ethanol and then benzene. The light-yellow product (37 mg.) had m.p. 151°–152° C. Calculated for $C_{25}H_{28}O_4N_4$: C, 66.94%; H, 6.29%. Found: C, 67.14%; H, 6.20%. (Melting point of 3-*O*-benzyl-D-glucose-phenylosazone 149°–150° C. (18).)

3-O-Benzyl-2-C-hydroxymethyl-D-glucono- and -D-mannono-γ-lactones (3-O-Benzyl-α- and -β-D-fructoheptonic lactones)

In preliminary tests, cyanohydration of 3-*O*-benzyl-D-fructose with aqueous sodium cyanide at pH 9.3 was approximately 95% complete within 40 hours' reaction time, as measured by evolution of ammonia after alkaline hydrolysis. Accordingly, 3-*O*-benzyl-D-fructose (14.7 g.) in water (25 ml.) was added to a solution (200 ml.) of sodium cyanide (4.1 g.) buffered to pH 9.3 with acetic acid. The pH of the solution rose rapidly to pH 9.8 and more acetic acid was added, further additions of the acid being required during the first 5 hours' reaction time to maintain the pH at 9.3. After 48 hours at room temperature, the reaction mixture was diluted with water (200 ml.) and then concentrated, water was added again and evaporated, the procedure being repeated three times, with the last evaporation at 70° C. to promote complete hydrolysis of the nitrile. The sirup obtained

was dissolved in water, treated with Amberlite IR-120, and the hydrocyanic and acetic acids released were removed upon evaporation. After the residue was heated at 100° C. *in vacuo* over phosphorus pentoxide for 4 hours, a pale yellow amorphous solid was obtained. Weight 11.1 g. The infrared absorption spectrum of the product showed a predominance of the γ-lactone form to be present (strong absorption band at 1770 cm.$^{-1}$ (30)). The product (46.5 mg.), in water, consumed 0.26 ml. of 0.1 *N* sodium hydroxide by direct titration to a stable end point. Excess of the alkali was added, the solution heated, and back-titrated with acid. The total alkali consumed was 1.57 ml. (required, 1.55 ml.), indicating that approximately 85% of the material existed as the γ-lactone.

*3-O-Benzyl-2-C-hydroxymethyl-*D*-mannono-γ-lactone* (*3-O-Benzyl-β-*D*-fructoheptonic lactone*)

Partial crystallization of the lactone mixture occurred after several months. The sirup was taken up in ethyl acetate and the crystals were filtered off and recrystallized from ethyl acetate. Weight, 120 mg. from 500 mg. of the mixture. Melting point 150.5°–152.0° C., $[\alpha]_D^{27}$ +45.5° (*c*, 1.2, alcohol). Calculated for $C_{14}H_{18}O_7$: C, 56.38%; H, 6.08%. Found: C, 56.16%; H, 6.05%. The compound absorbed strongly in the infrared region at 1770 cm.$^{-1}$, which, together with the stability exhibited to alkaline hydrolysis, showed the presence of a γ-lactone structure (30). The non-crystalline fraction showed $[\alpha]_D^{27}$ +89.3° (*c*, 1.6, alcohol).

The crystalline lactone was treated with one equivalent of hot sodium hydroxide solution; the resulting sodium salt showed $[\alpha]_D^{27}$ +11.6° (*c*, 1.4). This value was altered to $[\alpha]_D^{27}$ +15.4° (*c*, 1.3) by liberation of the free acid through addition of one equivalent of hydrochloric acid. Likewise, the salt and acid prepared from the non-crystalline material had $[\alpha]_D^{27}$ −1.1° (*c*, 1.9) and $[\alpha]_D^{27}$ −5.7° (*c*, 1.7), respectively. These data are in close agreement with the results obtained (31) by application of the salt–acid rule (11, 12) to α- and β-D-fructoheptonic lactones, and indicate that the crystalline lactone is the β-(*mannono*)-isomer.

3-O-Benzyl-2-C-(*hydroxymethyl*)-D-*arabo-hexitol*

The crude mixture of *O*-benzyl-D-fructoheptonic lactones (7.5 g.) in water (15 ml.) was added slowly to a solution of sodium borohydride (1.5 g.) in water (25 ml.) (19). After 2 hours, excess of acetic acid was added, the solution passed through a column of Amberlite IR-120, and the solvent evaporated. The resulting sirup was taken up in methanol, the methanol was evaporated, and this procedure repeated five times to ensure removal of boric acid. The product contained some free acid and lactone (infrared spectrum). Accordingly the material was neutralized in methanol with ethereal diazomethane, again treated with sodium borohydride, and the product was worked up as described above. A small quantity of acid and lactone still present was removed by dissolving the product in excess hot 0.05 *N* sodium hydroxide and then treating with a mixed-bed resin of Amberlite IR-120 and IR-4B. (Reduction of the lactone was more efficient when, in a separate run, the reaction was carried out in cold methanol in the presence of sodium methoxide (20).) The final product was a colorless glass which gave a single spot (R_{Rh} 1.9) on a paper chromatogram using the ammoniacal silver nitrate spray, and was shown by its infrared spectrum to contain neither carboxyl nor lactone groups; $[\alpha]_D^{25}$ +13.7° (*c*, 2.9, water). Weight 3.0 g. Calculated for $C_{14}H_{22}O_7$: C, 55.62%; H, 7.34%. Found: C, 55.66%; H, 7.34%.

2-C-(*Hydroxymethyl*)-D-*arabo-hexitol* ("D-*Fructoheptitol*")

The *O*-benzyl heptitol was dissolved in ethanol (20 ml.) and treated at ambient temperature and pressure with hydrogen in the presence of palladium black catalyst (0.10 g.).

Approximately 1 mole of hydrogen was taken up in 2 hours' reaction time; ultraviolet absorption analysis then showed complete absence of the benzyl group. Removal of the catalyst and evaporation of the solvent afforded a sirupy product having the same R_{Rh} (0.53) on a paper chromatogram as authentic "D-fructoheptitol" (21), and an infrared absorption spectrum indistinguishable from that of the latter compound. The material was acetylated with hot acetic anhydride – sodium acetate. The sirupy acetate formed gave an infrared absorption spectrum which, except for the added presence of a weak hydroxyl band, was indistinguishable from that of "D-fructoheptitol" heptaacetate (21), and had the same specific rotation; $[\alpha]_D^{25}$ +31.0° (*c*, 6.0, chloroform) (authentic material has $[\alpha]_D^{24}$ +31.6° (21)). The product crystallized with difficulty, however, and after repeated recrystallization from ethanol–water the acetate (10 mg.) melted at 63°–67° C., undepressed by admixture with an authentic specimen (69°–70° C.). The X-ray diffraction pattern of the compound was indistinguishable from that of "D-fructoheptitol" heptaacetate. Calculated for $C_{21}H_{30}O_{14}$: C, 49.80%; H, 5.97%; acetyl, 60.8%. Found: C, 50.15%; H, 6.35%; acetyl, 60.5%.

Glycol-Cleavage Oxidations of 3-O-Benzyl-2-C-(hydroxymethyl)-D-arabo-hexitol

Oxidation of the *O*-benzyl polyol was examined using excess lead tetraacetate in acetic acid and excess sodium metaperiodate in water. At intervals, aliquots were removed from each reaction mixture and the consumption of oxidant was measured: lead tetraacetate (moles per mole)—1.85 (10 minutes), 2.20 (25 minutes), 2.55 (40 minutes); periodate (moles per mole)—2.45 (5 minutes), 2.60 (15 minutes), 2.77 (25 minutes).

3-*C*-(*Hydroxymethyl*)-D-*glycero-tetrose* (D-*Apiose*)

3-*O*-Benzyl-2-*C*-(hydroxymethyl)-D-*arabo*-hexitol (1.5 g.) was dissolved in acetic acid (20 ml.) and lead tetraacetate (4.2 g., 1.9 molar equivalents) in acetic acid (140 ml.) was added. After the oxidant has been consumed, oxalic acid (0.8 g.) in acetic acid (8.0 ml.) was added with stirring, the precipitate was filtered off, and the solvent evaporated. The sirup was extracted with ethyl acetate and the extract concentrated yielding a sirup (1.0 g.) which was treated under reflux with methanolic hydrogen chloride (0.5%, 20 ml.) for 2 hours and at room temperature for 18 hours. Acid was removed with silver carbonate and the methanolic filtrate evaporated yielding a sirup (0.88 g.) non-reducing to Fehling's solution. The product was catalytically debenzylated as described above, and then hydrolyzed with 0.3 *N* sulphuric acid for 1 hour at 95° C. The hydrolyzate was neutralized with Dowex-1 resin (bicarbonate form) and concentrated. The resulting sirup (0.40 g.), which was found by paper chromatography to contain three components (R_{Rh} 1.3, 0.9, and 0.5, respectively), was chromatographed on a cellulose column (23) using *n*-butanol half-saturated with water. The fraction corresponding to D-apiose (R_{Rh} 0.9) was collected, filtered through a Seitz bacterial filter, and concentrated. The residue was taken up in water, and the solution filtered through charcoal and concentrated giving a clear colorless sirup (94 mg.); $[\alpha]_D^{25}$ +6.4° (*c*, 1.0, water). The infrared absorption spectrum was identical with that of D-apiose isolated from parsley. Treated with 2,5-dichlorophenylhydrazine according to the procedure of Bell *et al.* (6), the product (50 mg.) gave an osazone which after two recrystallizations from aqueous ethanol (weight 47 mg.) had m.p. 194°–195.5° C. (corr.) (Bell *et al.* (6) report m.p. 188.5°–190.5° C. for D-apiose-2,5-dichlorophenylosazone). The X-ray diffraction pattern of the osazone was identical with that of the 2,5-dichlorophenylosazone prepared from D-apiose isolated according to the procedure of Vongerichten (1) from parsley. Calculated for $C_{17}H_{16}O_3N_4Cl_4$: C, 43.80%; H, 3.46%. Found: C, 44.04%; H, 3.43%.

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SYNTHESIS OF SOME HEXANEDIOLS[1]

E. VON RUDLOFF

ABSTRACT

A general method for the preparation of 1,3-, 1,4-, and 1,5-hexanediols is described. The synthesis involves the preparation of a corresponding ketohexanoate, which is reduced to the diol with lithium aluminum hydride. Countercurrent distribution was found useful in the purification of small amounts of intermediates and end products. 1,2-, 1,6-, and 2,5-hexanediols were also prepared by known procedures. The infrared spectra of these diols have been recorded and their *p*-nitrobenzoates were prepared.

The analysis of mixtures of polyols obtained in the hydrogenolysis of methyl glucoside (1) required small amounts of various hexanediols for identification purposes. This paper describes a convenient method for preparing 3-, 4-, and 5-ketohexanoates, from which the 1,3-, 1,4-, and 1,5-hexanediols were obtained in 75–85% yield by lithium aluminum hydride reduction (2). It also describes the preparation of 1,2-, 1,6-, and 2,5-hexanediols by known procedures, and the preparation and characteristics of the *p*-nitrobenzoates. The infrared spectra of all of these hexanediols are recorded.

Hexanediols have been prepared by a variety of methods, none of which appeared to be generally applicable, and most suffered from the disadvantage that the starting materials were not readily available. Also, different types of crystalline derivatives were reported, making characterization by comparison difficult. No reference to the infrared spectra of these hexanediols could be found, although Kuhn (3) discusses the effect of hydrogen bonding on the infrared absorption band of the hydroxyl groups in 1,6-hexanediol.

The direct synthesis of hexanediols by general methods, such as the Grignard synthesis (4), did not appear feasible. A useful approach to their preparation appeared to be the synthesis of the corresponding keto- or hydroxy-acid (or ester), the latter being reduced readily to the hexanediol. When the synthesis of 4- and 5-ketohexanoic acids was attempted on a 10th molar scale by the methods of Winterfeld and Rönsberg (5), Yoho and Levine (6), and Perlin and Purves (7) only very low yields of rather impure keto-acids were obtained. Purification by fractional distillation on this scale proved unsatisfactory. The method of Cason *et al.* (8) for the preparation of keto-esters (III) was then modified according to Perlin and Purves and satisfactory results were obtained when the difficulties of purification of 5 to 10 g. reaction products had been overcome. The synthesis involves the preparation of a given carboxy acyl chloride (I), via the semi-ester of the dicarboxylic acid, which was reacted with the appropriate dialkyl cadmium (II). The latter was prepared in isopropyl ether (7) from the Grignard intermediate.

$$2R'O_2C.(CH_2)_n.COCl + CdR_2 \longrightarrow 2R'O_2C.(CH_2)_n.\underset{\underset{O}{\|}}{C}.R + CdCl_2$$

I II III

Provided the semi-ester was pure, the keto-ester was obtained in a satisfactory state of purity on fractional distillation. When the semi-ester was isolated impure (e.g. monoethyl malonate), neither the ketohexanoate nor the hexanediol could be purified satisfactorily

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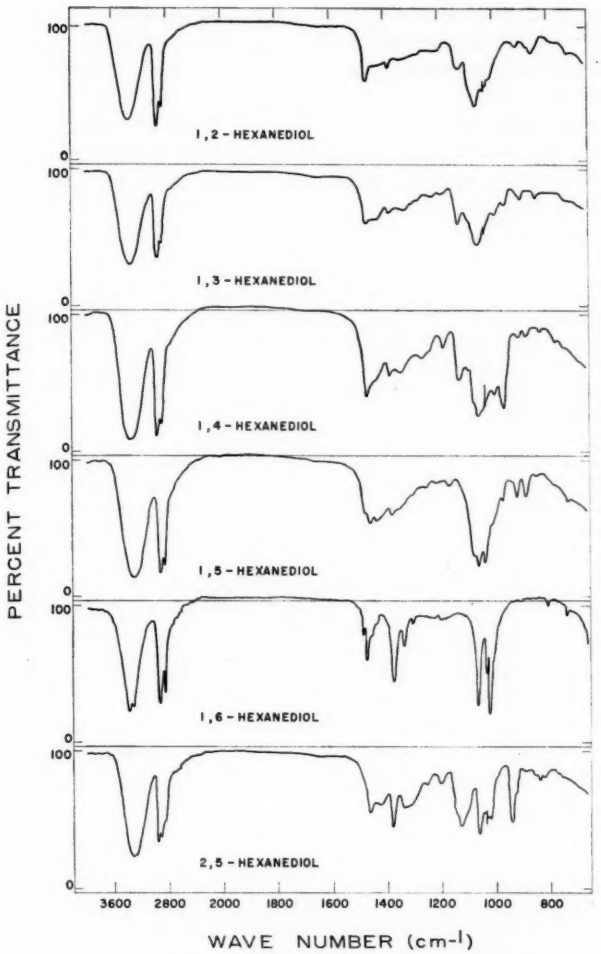

FIG. 1. Infrared spectra of hexanediols.

by fractional distillation. However, purification was possible by using countercurrent distribution. The distribution pattern of the keto-esters could not be obtained by weight analysis because of high solvent volatility. The impure keto-esters, therefore, were reduced and the reaction product was then fractionated and analyzed by countercurrent distribution, using weight analysis to obtain the distribution pattern. This analysis showed that the contaminant was the diol corresponding to the dicarboxylic acid component, indicating that the di-ester must have been present in the reaction mixture.

Reduction of the keto-esters with lithium aluminum hydride proceeded smoothly, and a good recovery of the products was obtained by salting out and extracting with ether containing 5–10% acetone. The use of methylal as solvent (9), as used in the reduction of adipic acid to 1,6-hexanediol, also gave satisfactory results. Catalytic reduction, as in the conversion of ethyl 5-ketohexanoate to 1,5-hexanediol in 85% yield by Hill and

Adkins (10), may sometimes be advantageous since the reaction can be carried out in ethanol or dioxane and larger quantities can be readily handled. The over-all yields of 1,5-, 1,4-, and 1,3-hexanediols were about 50%, 45%, and 30% respectively (based on the weight of semi-ester).

1,2-Hexanediol was prepared in about 45% over-all yield by α-bromination of caproic acid (11), hydrolysis to α-hydroxycaproic acid (12), and reduction with lithium aluminum hydride. Lithium aluminum hydride reduction of adipic acid (9) and acetonyl acetone gave 1,6- and 2,5-hexanediol, respectively, in better than 80% yield. 2,5-Hexanediol was also prepared in about 95% yield by catalytic hydrogenation of acetonyl acetone, using ethanol as solvent and copper chromium oxide as catalyst (10, 13).

Previously, it was found that hexanediols give a better yield of the *p*-nitrobenzoate than of the 3,5-dinitrobenzoate (1). Since the *p*-nitrobenzoates of hexanediols are crystalline compounds with high melting points, these were prepared as suitable derivatives. The 1,3-isomer was dimorphous, a phenomenon which was also observed with the *p*-nitrobenzoate of 1,3-propanediol.

The infrared spectra of the individual hexanediols (see Fig. 1), except those of 1,2- and 1,3-hexanediol, differ sufficiently from each other to allow identification. No significant differences were found in the spectra of the *p*-nitrobenzoates.

EXPERIMENTAL

All melting points are corrected and were measured with a Leitz heating stage microscope. The infrared spectra were recorded with a Perkin Elmer model 21 spectrometer equipped with a sodium chloride prism. Liquid compounds were mounted by the suspended film technique and solids by the potassium bromide disk technique (14). Countercurrent distribution was carried out with a 100 tube modified E.C. Apparatus Co. fractionator having 40 ml. tube capacity (20 ml. upper and 20 ml. lower phase). *p*-Nitrobenzoates were prepared by the Schotten–Baumann reaction, using pyridine as base and solvent (15), and they were recrystallized from ethyl acetate – petrol and 2-butanone–petrol (b.p. 64°–66° C.).

Semi-esters of Dicarboxylic Acids

Succinic anhydride and glutaric anhydride were prepared by refluxing the dicarboxylic acids with excess acetic anhydride (16). The anhydrides were then converted to the monomethyl esters by the method of Ruggli and Maeder (17), e.g. succinic anhydride, 25 g. (0.25 mole), was refluxed with absolute methanol, 20 ml., for ½ to 1 hour. The excess methanol was removed by evaporation in a rotary evaporator and the residue cooled to about 5° C., when it solidified. The crude material was recrystallized three times from ether to give monomethyl succinate, 29 g. (88% of theory), m.p. 58° C. Monomethyl glutarate was obtained similarly in about 80% yield and was purified by fractional distillation, b.p. 153°–155° C. at 10–11 mm.

Monoethyl malonate was prepared by saponification of the diethyl ester with the theoretical amount of potassium hydroxide (18). Diethyl malonate, 50 g. (0.31 mole), in 200 ml. absolute ethanol was added slowly to a solution of potassium hydroxide, 17.5 g. (0.31 mole), in 200 ml. absolute ethanol. The mixture was allowed to stand at room temperature until it was neutral. It was then heated and filtered hot. The potassium salt crystallized rapidly and after crystallization was complete it was filtered off, washed twice with cold ethanol and once with ether. The crystalline product was dissolved in a minimum of water and acidified in the cold with concentrated hydrochloric acid. On

standing, a little malonic acid crystallized, which was filtered off. The aqueous solution was then extracted repeatedly with ether. The ethereal extracts were washed once with water and then dried over anhydrous sodium sulphate. When the dried ethereal solution was reduced to a small volume, more malonic acid crystallized. The residue from evaporation of the filtered ethereal solution was fractionally distilled *in vacuo*, to give 29 g. monoethyl malonate (about 70% of theory), b.p. 131°–133° C. at 11–12 mm.

Synthesis of Ketohexanoates

The following is a typical example of the procedure adopted for the preparation of methyl or ethyl 3-, 4-, and 5-ketohexanoate.

To monomethyl succinate, 13.2 g. (0.10 mole), was added thionyl chloride (reagent grade), 15 g. (0.125 mole), and the mixture was left at room temperature under a reflux condenser equipped with a calcium chloride tube. After the evolution of gas had subsided, the solution was heated at 40°–45° C. for 3 to 6 hours and was left at room temperature for a further 16 hours. Excess thionyl chloride was then removed on a rotary evaporator at 15 mm. and 40°–45° C. (17). The residual acid chloride was dissolved without further purification in 25 ml. dry, peroxide-free isopropyl ether and added dropwise with stirring to a cooled mixture of the dialkyl cadmium. The latter mixture was prepared by reacting magnesium, 3.6 g. (0.15 g. atom), in isopropyl ether (7), 60–65 ml., with dry ethyl bromide, 17.4 g. (0.16 mole), in 25 ml. isopropyl ether in the normal Grignard manner, and adding to the cooled solution with vigorous stirring anhydrous cadmium chloride (dried in a vacuum oven at 70° C. for 18 to 24 hours), 14.7 g. (0.08 mole), in one portion.

After addition of the acid chloride was complete, the mixture was refluxed with stirring for 3 to 4 hours and was left at room temperature for 16 hours, and was then poured into excess ice and 10% sulphuric acid. The aqueous layer was separated and extracted three times with an equal volume of ether. The ethereal extracts were added to the isopropyl ether layer and the combined solution was washed once with 5% sodium bicarbonate solution, twice with water, and dried over anhydrous sodium sulphate. On evaporation of the ether a light brown liquid was obtained. It was distilled *in vacuo* and the fraction of b.p. 75°–78° C. at 11–12 mm. was collected. The yield of impure methyl 4-ketohexanoate was 9 g. (63% of theory).

Attempts to purify the keto-esters thus obtained by fractional distillation were unsuccessful, presumably because of the small amounts available. Countercurrent distribution, using 40 to 70% ethanol and petrol b.p. 64°–66° C. as solvent pair, gave a satisfactory separation, but about one-half of the keto-esters was lost on evaporation of the solvents. In this manner methyl 5-ketohexanoate, b.p. 100°–101° C. at 11–12 mm., was obtained in 20–25% over-all yield. Calc. for $C_7H_{12}O_3$: C, 58.31; H, 8.39%; saponification equivalent 144.17. Found: C, 58.17; H, 8.45%; saponification equivalent 145.

Reduction to Hexanediols

A solution of impure methyl 4-ketohexanoate, 4.3 g. (0.03 mole), in dry ether, 50 ml., was added dropwise with stirring to a suspension of lithium aluminum hydride, 1.9 g. (0.05 mole), in dry ether, 100 ml., which had been refluxed previously for ½ to 1 hour. The usual precautions against moisture were taken. The mixture was refluxed for ½ to 1 hour after addition of the ester, and, after cooling, ice water was added dropwise until excess lithium aluminum hydride had reacted. To the cold mixture was added cold 10% sulphuric acid, 10–20 ml., and after the mixture had cleared, it was saturated with potassium carbonate. The ether layer was withdrawn after adding 10 to 15 ml. acetone. The aqueous layer was then extracted exhaustively with ether containing 5–10% acetone. The ethereal

extracts were dried first over anhydrous potassium carbonate and then over anhydrous sodium sulphate. On evaporation of the ether, impure 1,4-hexanediol, 2.8 g. (80% of theory), was obtained. The mixture, 1.87 g., was fractionated by countercurrent distribution, using 2-butanone–water as solvent pair and 70 transfers. The distribution pattern was obtained by evaporating every second tube and weighing the residue in 20-ml. porcelain crucibles. Tubes 9–26 contained a viscous liquid, 0.45 g., which had an infrared spectrum identical to that of 1,4-butanediol. Calc. for $C_4H_{10}O_2$: C, 53.23; H, 11.49%. Found: C, 53.31, H, 11.19%. The *p*-nitrobenzoate, m.p. 175°–176° C., was undepressed in a mixture with an authentic specimen (m.p. 175°–176° C.). Tubes 28–40 contained 1,4-hexanediol, 1.25 g. The analytical data for this, as well as all the other hexanediols and their *p*-nitrobenzoates, are summarized in Table I.

TABLE I

	Hexanediols				*p*-Nitrobenzoates			
	B.p. at 0.3 mm. (air bath), ° C.	n_D^{20}	% C*	% H	M.p., ° C.	% C†	% H	% N
1,2-[1]	75–80	1.4431	61.11	11.75	101.5–102.5	57.79	4.87	6.63
1,3-[2]	85–90	1.4455	60.91	11.84	78–79 and 93–95.5	57.50	4.88	6.71
1,4-[3]	75–80	1.4515	60.93	11.97	124.8–125.4	57.55	4.82	6.72
1,5-[4]	85–90	1.4490	60.94	12.10	103.5–104.2	57.63	4.72	6.62
1,6-[5]	m.p. 41.0–41.8	—	61.23	12.10	121.8–122.5[6]	57.77	4.80	6.71
2,5-[7]	80–85	1.4474	60.92	11.87	170.0–171.0	57.79	4.86	6.48

**Calculated for $C_6H_{14}O_2$: C, 60.98; H, 11.94%.*
†Calculated for $C_{20}H_{20}N_2O_8$: C, 57.69; H, 4.84; N, 6.73%.
[1]Levene and Haller (19): b.p. 110°–131° C. at 6 mm. (dinaphthylurethan m.p. 172°–174° C.).
[2]Glacet (20): b.p. 123°–123.4° C. at 13 mm., n_D^{22} 1.4461 (diphenylurethan m.p. 99.3° C.).
[3]Glacet (20): b.p. 127.5°–127.7° C. at 13 mm., $n_D^{16.3}$ 1.4530 (diphenylurethan m.p. 71° C.).
[4]Hill and Adkins (10): b.p. 89°–91° C. at 0.5 mm.
[5]Haworth and Perkin (21): b.p. 152° C. at 17 mm.; m.p. 42° C.
[6]Heyns and Woyrsch (22): m.p. 120° C.
[7]Duden and Lemme (23): b.p. 120°–122° C. at 12 mm.; n_D^{20} 1.4475.

In the same manner 1,5-hexanediol and 1,3-hexanediol were obtained in about 50% and 30% over-all yield respectively. In addition to 1,3-hexanediol, a considerable amount of 1,3-propanediol, *p*-nitrobenzoate, m.p. 109°–111° C. and 117°–118.5° C., mixed m.p. with an authentic specimen 111°–112° C. and 117°–118.5° C., was isolated.

Lithium aluminum hydride reduction of α-hydroxycaproic acid, adipic acid (9), and 2,5-hexanedione (acetonyl acetone) gave 1,2-, 1,6-, and 2,5-hexanediol respectively in 75–85% yield. α-Hydroxycaproic acid, m.p. 60°–62.5° C., was prepared in about 60% over-all yield by α-brominating caproic acid (11) and hydrolyzing the α-bromocaproic acid with aqueous potassium carbonate (12). Adipic acid, m.p. 151°–153° C., and 2,5-hexanediol, b.p. 192°–194° C., were obtained commercially. 2,5-Hexanediol was also prepared in better than 90% yield by hydrogenation over copper chromium oxide according to the method of Hill and Adkins (10).

ACKNOWLEDGMENTS

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THE COMPOUND $CaO.Ti_2O_3$[1]

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ABSTRACT

By electrolyzing baths of molten $CaCl_2$ containing perovskite ($CaO.TiO_2$), a compound within the ternary Ca–Ti–O system, namely $CaO.Ti_2O_3$, has been obtained. The compound has been identified by chemical analysis, and its crystallographic data have been determined by X-ray means. Attempts to synthesize the compound apart from the electrolytic cell have, so far, failed.

INTRODUCTION

The only publications of work dealing with compounds within the ternary system Ca–Ti–O in which the titanium is in any state of valency other than the tetravalent are those of Bertaut and Blum (1, 2). In their work, the crystallography of a compound, to which is assigned the formula $CaTi_2O_4$, is described. The system $CaO–TiO_2$ has been studied by von Wartenberg, Reusch, and Saran (3), and their work did not indicate the existence of any compound between $CaO.TiO_2$ and TiO_2, but merely of a eutectic having a melting point of approximately 1450° C.; further, there was no indication in their work of any compound containing a lower proportion of oxygen.

In the course of work on the electrochemistry of the production of titanium, a material was encountered which forms the subject of this paper. The material was examined by chemical, X-ray diffraction, and spectrographic means and has been shown to be $CaTi_2O_4$ (or $CaO.Ti_2O_3$); some of its properties have been determined. This work was done independently and without the knowledge of the work of Bertaut and Blum. Their work was entirely crystallographic, whereas, as mentioned above, the present work includes chemical data.

EXPERIMENTAL

(*a*) *Preparation of the Compound*

When a bath composed of 300 g. of calcium chloride and containing 60 g. of calcium titanate, $CaO.TiO_2$, which is slightly soluble in the molten chloride, was electrolyzed under an inert atmosphere for 70 minutes at a current of 14 amp. at 850° C. and allowed to cool, some black, lustrous, well-formed crystals were observed close to the cathode.

(*b*) *Chemical Examination of the Compound*

Examination of the crystals under a low-power microscope showed them to be prismatic in form and very well developed. No difficulty was experienced in selecting suitable specimens for detailed X-ray crystallographic examination.

The examination of the material by semiquantitative spectrographic analysis showed that Ca and Ti were the only detectable major metallic constituents.

About 60 mg. of the material was available for chemical analysis, and the determinations shown in Table I were made.

The methods used for analysis were as follows:

Calcium.—Determined with a Perkin–Elmer flame photometer at 6200 Å, after

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TABLE I

Element	% by weight
Ca	20.3±0.2
Ti	47.0±0.1 (all trivalent)
Fe	1.05±0.05 (mean of two determinations)
C	0.07±0.02
F	None detectable

removal of iron and titanium as "cupferrides", aluminum as 8-hydroxyquinolate, and after removal of excess organic reagents.

Iron.—Determined in the chloroform solution of the "cupferride" by colorimetric means with *o*-phenanthroline, using a Coleman MK.14 spectrophotometer at $\lambda = 500\ \mu\mu$.

Titanium.—Determined in the chloroform solution of the "cupferride" by colorimetric means with hydrogen peroxide, using a Coleman MK.14 spectrophotometer at $\lambda = 410\ \mu\mu$. This gives the total titanium. The trivalent titanium was determined by dissolving the sample in aqueous sulphuric acid, and titrating against standard ferric alum, all under an argon atmosphere.

Carbon.—Determined by a standard combustion procedure.

Fluorine.—HF steam-distilled off at 135°–140° C. from an aqueous perchloric acid suspension of the sample. Fluoride estimated amperometrically at pH = 7.0 using thorium nitrate solution previously standardized against NaF.

The unestimated material, approximately 31.6%, is presumably oxygen since no major constituent other than calcium and titanium was detectable spectrographically.

An X-ray powder diffraction pattern of the crushed material was taken using CoK_α radiation and a 57.3 mm. diameter Debye-Scherrer camera. The pattern was well defined, but could not be identified by reference to either the A.S.T.M. Card Index of X-Ray Diffraction Patterns or any other source of data available to the authors.

The material showed slight signs of ferromagnetism, and certain weak lines in the X-ray diffraction pattern could be interpreted as being due to the presence of a small amount of metallic iron. It was considered, therefore, that the iron in the above chemical analysis is probably due to the presence of a small quantity of free metallic iron and that the main compound is essentially a calcium–titanium–oxygen compound. On this basis, the observed and theoretical compositions and atomic ratios of the relevant compounds are as follows:

	Ca	Ti	O
Observed	20.3±0.2%	47.0±0.1%	31.6±0.3% (by difference)
Atomic ratios	1.000	1.937±0.015	3.900±0.075
Calculated for $CaTi_2O_4$	20.1%	47.9%	32.0%
Calculated for $CaTi_2O_5$	18.6%	44.4%	37.0%

It thus seems reasonable to conclude that the compound represented by our data is, in fact, $CaO.Ti_2O_3$. It must, however, be borne in mind that the above chemical analyses were made on very small quantities of material and, in any case, the analytical procedures were not simple.

The limits of error quoted in Table I are merely those of the final stage of each estimation; with the very small quantities of material available for investigation there was no

TABLE II

Data	Present work	Data of Bertaut and Blum
Crystal system	Orthorhombic	Orthorhombic
Cell dimensions, Å	$a_0 = 9.73$	9.727
	$b_0 = 9.99$	9.976
	$c_0 = 3.14_7$	3.136
Z	4	4
Space group	$Bbmm-D_{2h}^{17}$ (V_h^{17})	$Bbmm-(D_{2h}^{17})$

TABLE III

X-RAY POWDER DIFFRACTION DATA FOR $CaO.Ti_2O_3$

Intensities assessed visually with strongest line as 100. Calculated d-spacings based on orthorhombic unit cell having dimensions $a = 9.73$, $b = 9.99$, $c = 3.14_7$ Å

Int.	d (meas.)	d (calc.)	($hk!$)	Int.	d (meas.)	d (calc.)	($hk!$)
		4.99	020	10	1.610	1.621	600
20	4.96	4.86	200	10	1.594	1.600	610
20	2.985	2.994	101			1.575	260
30	2.858	2.868	111	70	1.569	1.574	002
100	2.742	2.747	230			1.571	521
30	2.556	2.568	121			1.544	450
10	2.489	2.498	040	10	1.531	1.542	620
20	2.418	2.431	400			1.501	022
10	2.379	2.362	410	30	1.493	1.497	202
30	2.244	2.258	301			1.496	351
20	2.213	2.222	240			1.482	531
90	2.196	2.202	311	20	1.478	1.481	212
10	2.166	2.186	420			1.457	630
80	2.052	2.058	321	30	1.458	1.455	161
10	1.947	1.964	430	10	1.428	1.434	222
30	1.906	1.918	141	—	—	1.379	541
20	1.869	1.869	331	—	—	1.374	460
20	1.837	1.848	250			1.369	270
10	1.742	1.742	440	40	1.370	1.365	232
10	1.681	1.675	341		1.362	1.360	640
		1.665	060	10	1.345	1.340	361
80	1.658	1.662	151	20	1.321	1.331	042
		1.654	501			1.321	402
20	1.632	1.632	511	10	1.305	1.310	412

ready means of assessing the errors of the various stages of separation involved in these analyses; hence it is possible that the estimations, considered as a whole, may be subject to somewhat larger errors than those quoted. This being the case, a molecular formula of $CaO.2TiO_2$ (i.e., $CaTi_2O_5$) is regarded as very unlikely but not entirely impossible. Such a formula would be analogous to that of magnesium dititanate, $MgO.2TiO_2$, which is a well-established compound. This supposition is, however, in conflict with the work of von Wartenberg *et al.* (3).

Several attempts were made to synthesize both $CaO.Ti_2O_3$ and $CaO.2TiO_2$ by sintering suitable mixtures of the constituent oxides at high temperature under appropriate atmospheric conditions. In neither case was any success achieved, and all the results obtained confirmed the work of von Wartenberg *et al.*

In general, however, it may be said that the chemical evidence supports the formula $CaO.Ti_2O_3$ for the material which forms the subject of the present study, rather than the formula $CaO.2TiO_2$.

(*c*) *Crystallographic Studies of the Compound*

The following morphological data were obtained as the average of observations on two well-formed crystals, using a standard two-circle optical goniometer:

Crystal class: orthorhombic.

Axial ratio: $a:b:c = 0.916:1:0.308$.

The single crystal X-ray work included rotation photographs, zero-layer and first-layer Weissenberg photographs, and cone-axis, zero-level, and first-level precession photographs. The Weissenberg photographs were made using CoK_α radiation, with rotation about the prismatic axis, and the precession photographs were made using MoK_α radiation, with the prismatic axis as the dial axis. The cell edges were determined from these photographs; from the systematic extinctions, the space group was obtained. The results of these examinations are given in Table II.

The space group quoted is the same as for the mineral pseudobrookite, $Fe_2O_3.TiO_2$ (i.e. $TiFe_2O_5$), and for the isomorphous compound magnesium dititanate, $MgO.2TiO_2$ (i.e. $MgTi_2O_5$), referred to earlier.

The powder diffraction pattern was indexed according to our cell dimensions, as shown in Table III, and the agreement between the observed and calculated spacings is quite good; also, the axial ratios determined by optical goniometry agree well with those determined by X-ray diffraction.

DISCUSSION OF RESULTS

It has thus been possible to describe the crystallography of this compound, to which is assigned the formula $CaO.Ti_2O_3$, in a reasonably complete fashion, and to provide a chemical analysis of sufficient accuracy to indicate the molecular formula with virtual certainty, even though it was not found possible to synthesize it apart from the electrolytic method in which it was first prepared. In the work of Bertaut and Blum, the material was obtained by the electrolysis of TiO_2 in molten $CaCl_2$. Their formula is based entirely on X-ray crystallographic evidence. There is good agreement between their X-ray results and those obtained in the course of the present work. The formula, $CaTi_2O_4$, quoted by them is also in good accord with our chemical data. The fact that the titanium is in the trivalent condition, as shown by the chemical analysis, indicates that this compound is best represented by the formula $CaO.Ti_2O_3$. Thus, the present work gives additional data on the electrolytic conditions of preparation of this compound and on its chemical composition, while providing good confirmation of the X-ray crystallographic work of Bertaut and Blum.

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AMINO ACIDS

IV. THE REACTION OF GLYCINE AND β-ALANINE WITH CARBON DISULPHIDE[1]

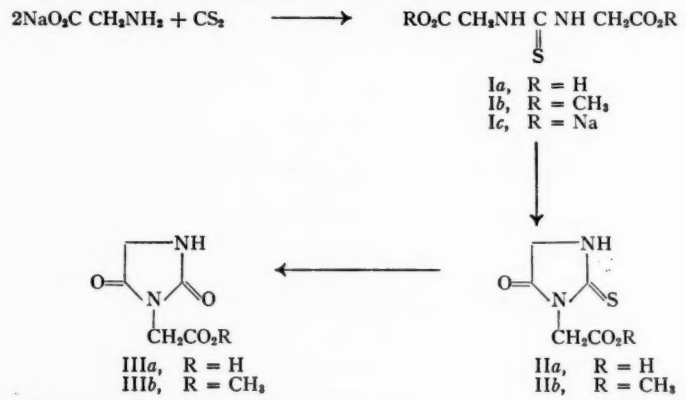
E. J. TARLTON AND A. F. MCKAY

ABSTRACT

Glycine and β-alanine on condensation with carbon disulphide gave the corresponding 1,3-di-(carboxyalkyl) thioureas. 1,3-Di-(carboxymethyl) thiourea is rearranged to 2-thio-3-(carboxymethyl) hydantoin by warming with hydrochloric acid solution or heating above its melting point. Evidence is presented for the reversible condensation of 2 mole equivalents of the sodium salt of 2-thio-3-(carboxymethyl) hydantoin by the elimination of water. This condensation product is obtained as well-defined pink crystals. 1,3-Di-(β-carboxyethyl) thiourea was oxidized with an alkaline solution of hydrogen peroxide or sodium hypochlorite solution to 1,3-di-(β-carboxyethyl) urea. 1,3-Di-(β-carboxyethyl) thiourea and 1,3-di-(β-carboxyethyl) urea have been cyclized by heating with *p*-toluenesulphonic acid. The products were 2-thio-3-(β-carboxyethyl) hydrouracil and 3-(β-carboxyethyl) hydrouracil respectively.

The reaction of several α-amino acids and carbon disulphide in aqueous sodium bicarbonate solution has been studied earlier by Kodama (1, 2). In most cases, he found that the only identifiable products were substituted thiohydantoins, which presumably were formed by cyclization of the intermediate 1,3-di-(carboxymethyl) thioureas. In the reaction with glycine, however, no distinct products were obtained although the copious evolution of hydrogen sulphide indicated that condensation had occurred. The reaction has now been reinvestigated in conjunction with the condensation of glycine and its homologue, β-alanine, with carbon disulphide.

Sodium glycinate and carbon disulphide were condensed in aqueous solution to yield the crude disodium salt of 1,3-di-(carboxymethyl) thiourea (I*c*). Reaction of this disodium salt with methanolic hydrogen chloride at room temperature gave 1,3-di-(carbomethoxymethyl) thiourea (I*b*) in 25% yield. The combined mother liquors on treatment with concentrated hydrochloric acid gave 2-thio-3-(carboxymethyl) hydantoin (II*a*) (m.p. 214°–215° C. dec.) in 17% yield. The latter compound was identified by analysis and by desulphurization with aqueous chloroacetic acid, to the known 3-(carboxymethyl) hydantoin (III*a*) and methyl ester of 3-(carboxymethyl) hydantoin (III*b*) (3). The methyl ester of 2-thio-3-(carboxymethyl) hydantoin (II*b*) melted at 113°–114° C.



[1]*Manuscript received November 20, 1957.*
Contribution from the L. G. Ryan Research Laboratories of Monsanto Canada Limited, Montreal, Quebec.

Careful saponification of the dimethyl ester (I*b*) gave 1,3-di-(carboxymethyl) thiourea (I*a*) which melted at 164°–165° C. with loss of 1 mole of water and resolidified to form 2-thio-3-(carboxymethyl) hydantoin which then melted at 214°–215° C. with decomposition. 1,3-Di-(carboxymethyl) thiourea was previously reported (4) as melting at 170° C. with decomposition. In concurrence with previous work (4, 5) this thiourea diacid (I*a*), its dimethyl ester (I*b*), and disodium salt (I*c*) all cyclize in acid solution to give 2-thio-3-(carboxymethyl) hydantoin. As a preparative method, the reaction mixture of crude disodium 1,3-di-(carboxymethyl) thiourea (I*c*) on brief treatment with concentrated hydrochloric acid gave the thiohydantoin (II*a*) in 48% yield.

When the condensation of sodium glycinate and carbon disulphide was conducted in the usual manner and the reaction mixture was acidified at room temperature to a pH of 2 with hydrochloric acid, no precipitation of product occurred. However, the solution yielded an orange-colored product (V)[2] melting at 287°–290° C. with decomposition. A 23% yield of 2-thio-3-(carboxymethyl) hydantoin (II*a*) was obtained from the mother liquors. In another experiment, the high melting condensation product (V) appeared in 31% yield on acidification of the reaction mixture with 2.2 moles of hydrochloric acid, followed by subsequent evaporation and extraction. In this case, the residue from the mother liquors gave on methylation 2-thio-3-(carbomethoxymethyl) hydantoin (II*b*) in 7% yield. The colored condensation product (V) proved to contain chemically bound sodium but it gave a negative halogen test. Potentiometric titration of the compound in aqueous solution with standard alkali showed it to be an acid with a primary pK_a of 3.4 and a neutralization equivalent of 373, which agrees with the acid equivalent (374.31) of the empirical formula $C_{10}H_8N_4O_5S_2Na_2$. Attempts to methylate this product with methanolic hydrogen chloride gave 2-thio-3-(carbomethoxymethyl) hydantoin (II*b*) in 81% yield. Brief treatment of the condensation product (V) with concentrated hydrochloric acid gave an 84% yield of 2-thio-3-(carboxymethyl) hydantoin (II*a*), while desulphurization with aqueous chloroacetic acid followed by methylation gave 3-(carbomethoxymethyl) hydantoin (III*b*) in 25% yield. Other attempted alkylation experiments with benzyl chloride or dimethyl sulphate in the presence of aqueous base led to the isolation of 2-thio-3-(carboxymethyl) hydantoin (II*a*) and not to a derivative of the condensation product (V). Empirically, these observations indicate the condensation product (V) to be the result of an easily reversible condensation of 2 moles of the sodium salt of 2-thio-3-(carboxymethyl) hydantoin with the elimination of 1 mole of water in such a way as to leave a titratable acid function in the product. Potentiometric titration data on 2-thio-3-(carboxymethyl) hydantoin (II*a*) and the colored condensation product add additional evidence to this hypothesis.

The titration of 2-thio-3-(carboxymethyl) hydantoin (II*a*) (Fig. 1, curve A) with 0.1 *N* sodium hydroxide solution gave a typical titration curve for an acid (pK_a 3.2) with an observed neutralization equivalent of 173 (calculated, 174). At the neutralization point (n_1) the color of the solution changed from yellow to red-orange. The solution was then back-titrated with standard hydrochloric acid (Fig. 1, curve B). Again, at the neutralization point (n_2), a color change of red-orange to orange occurred. Curves A and B do not coincide and it will be observed that if the amount of sodium hydroxide solution (0 to n_1) required to neutralize 2-thio-3-(carboxymethyl) hydantoin (II*a*) is 1 mole, then the difference between n_1 and n_2 is 0.5 mole. This can be explained by consideration of the following reaction sequence:

[2]*This product is referred to hereafter as condensation product.*

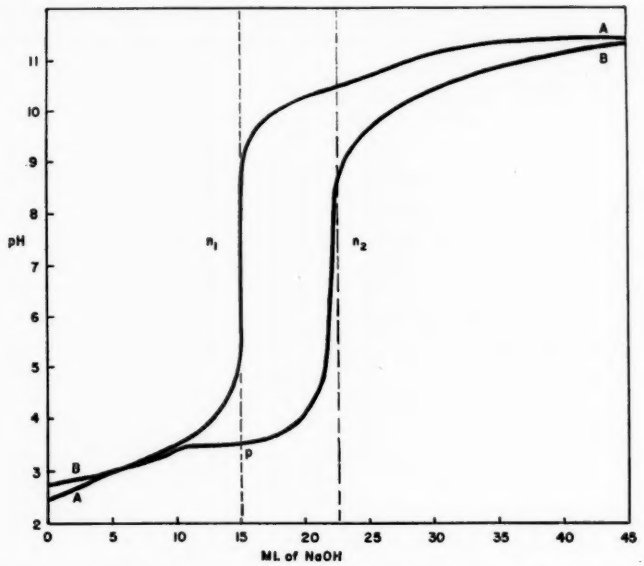


FIG. 1. Titration (*A*) and back-titration (*B*) of 2-thio-3-(carboxymethyl) hydantoin (II*a*) in aqueous solution.

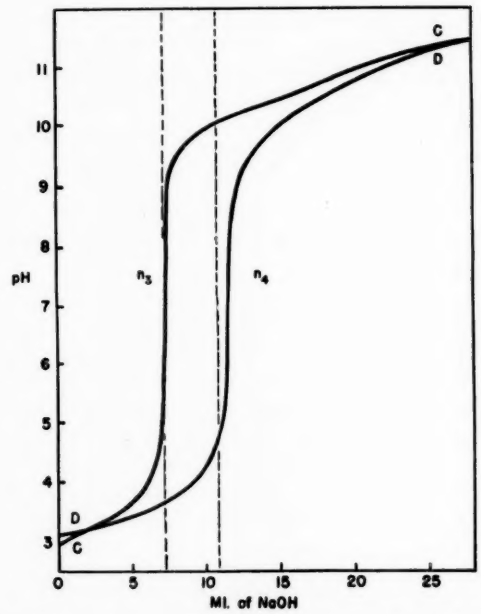


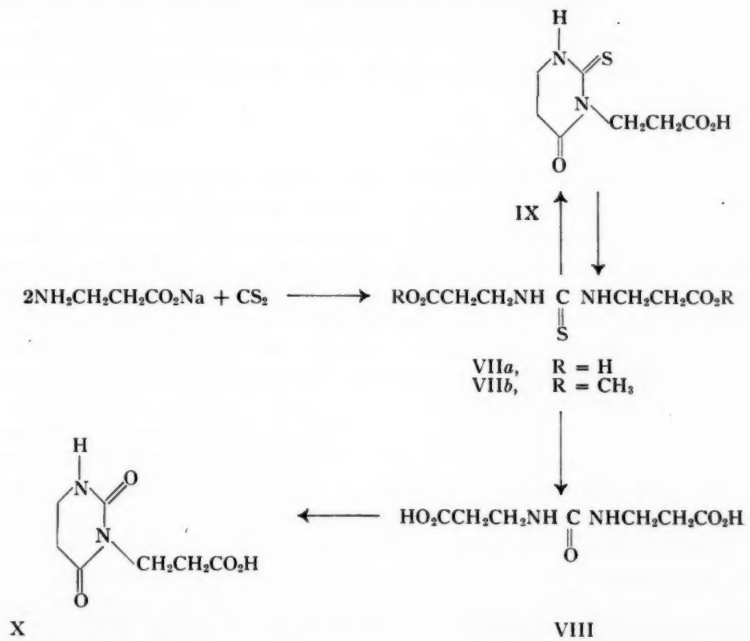
FIG. 2. Titration (*C*) and back-titration (*D*) of condensation product (V) in aqueous solution.

$$\text{IIa} \xrightarrow[\text{OH}^-]{\text{OH}^-} \text{Monosodium salt of IIa (IV)} \xrightarrow{-H_2O} \text{Condensation product } (C_{10}H_8N_4O_5S_2Na_2)\ \text{(V)}$$
$$\rightleftharpoons[H^+]{} \text{Sodium salt of condensation product } (C_{10}H_7N_4O_5S_2Na_3)\ \text{(VI)}.$$

Following curve A, the conversion of 2-thio-3-(carboxymethyl) hydantoin (II*a*) into its monosodium salt (IV) is complete at n_1; at n_1, IV undergoes self-condensation with elimination of water to give the condensation product (V), which is in turn neutralized to give VI. The neutralization of V to VI requires 1 mole of base per mole of condensation product or *one-half the amount of base required to neutralize IIa originally*. On the back-titration curve B, the conversion of VI to V begins at n_2 and should be complete at p. The validity of this interpretation rests on the isolation of the condensation product (V) from the solution used in the titration and back-titration of II*a*. Experimentally, this method gave an 80% conversion of II*a* into V. The analytical values obtained for the condensation products prepared by the two methods agreed within experimental error. However, in both cases the values obtained for hydrogen were higher than the value calculated for the empirical formula $C_{10}H_8N_4O_5S_2Na_2$.

The titration and back-titration of the condensation product (V) gave the same result (Fig. 2). Again, the difference between the two curves (C and D) at n_3 and n_4 represents approximately one-half the amount of base required to reach n_3. In analogy with the titration experiments on 2-thio-3-(carboxymethyl) hydantoin (II*a*), it appears that the condensation process has again occurred.

Although there is not sufficient evidence to formulate the structure of the condensation product (V) with its two combined sodium atoms, the data suggest that the product has a free carboxyl group and that the sodium atoms are bound as salts of an enolic structure. Furthermore, the structure of the initial condensation product (V) must be such that the same mode of self-condensation can be repeated.



The condensation of sodium β-alaninate and carbon disulphide proceeded normally. The product, 1,3-di-(β-carboxymethyl) thiourea (VII*a*), proved to be very water soluble and hence was isolated in the form of its dimethyl ester (VII*b*) in 56% yield. Saponification of the diester (VII*b*) in aqueous base readily gave the diacid (VII*a*). This thiourea–diacid (VII*a*) was oxidized with 4 moles of aqueous sodium hypochlorite or hydrogen peroxide in the presence of 4 moles of base to 1,3-di-(β-carboxyethyl) urea (VIII).

There are numerous examples in the literature of the cyclization of β-thioureido and β-ureido alanines to hydrouracil and its derivatives. This was accomplished by the cyclizing action of acetic anhydride, hydrochloric acid, or simply heat (6, 7, 8, 9, 10, 11) on the β-ureido alanines, while others (12, 13, 14) found that the corresponding esters undergo ring closure in the presence of sodium alkoxides. When 1,3-di-(β-carboxyethyl) thiourea (VII*a*) was heated with *p*-toluenesulphonic acid at 160°–175° C., 2-thio-3-(β-carboxyethyl) hydrouracil (IX) was obtained in 85% yield. In accordance with observations on other hydrouracil derivatives (7, 15) this process was easily reversed by the action of warm aqueous base on IX. Similarly, the action of hydrochloric acid or acetic anhydride on 1,3-di-(β-carboxyethyl) urea (VIII) gave 3-(β-carboxyethyl) hydrouracil (X).

As a preparative method, the 2-thio-3-(β-carboxyethyl) hydrouracil (IX) can be prepared in 46% yield from the crude 1,3-di-(β-carboxyethyl) thiourea (VII*a*) by cyclization with *p*-toluenesulphonic acid. It is of interest to note that the cyclization of 1,3-di-(carboxymethyl) thiourea (I*a*) to yield 2-thio-3-(carboxymethyl) hydantoin (II*a*) is more facile than the ring closure of its homologue (VII*a*) to the thiohydrouracil (IX). This is demonstrated by the behavior of the two compounds on fusion. As noted above, 1,3-di-(carboxymethyl) thiourea (I*a*) loses water readily at its melting point while VII*a* remains unchanged under these conditions.

During the investigation of the cyclization of 1,3-di-(β-carboxyethyl) thiourea (VII*a*) with acetic anhydride under reflux, desulphurization as well as cyclization occurred. The product, 3-(β-carboxyethyl) hydrouracil (X), was obtained in 26% yield. To our knowledge, the desulphurization of a thiohydrouracil with acetic anhydride has not been observed previously.

EXPERIMENTAL[3]

1,3-Di-(carboxymethyl) Thiourea and 2-Thio-3-(carboxymethyl) Hydantoin

A stirred mixture of glycine (20 g., 0.26 mole), carbon disulphide (10.2 g., 0.13 mole), and water (20 ml.) was treated dropwise with a solution of sodium hydroxide (10.68 g., 0.26 mole) in water (27 ml.) over a period of 15 minutes. After the initial heat effect had abated additional carbon disulphide (2 g.) was added and the solution was held at the reflux temperature of carbon disulphide for 30 minutes. The excess carbon disulphide was evaporated and the remaining solution was refluxed for 7 hours. During this latter heating stage copious evolution of hydrogen sulphide occurred. The solution was cooled, filtered, and divided into two equal portions.

One portion of the solution was evaporated to dryness *in vacuo* on the steam bath and the residual viscous red oil was dried *in vacuo* over potassium hydroxide pellets. This residue was treated with 10% methanolic hydrogen chloride solution (100 ml.) at room temperature. A pale yellow solution containing some insoluble crystals of sodium chloride was obtained. Methylation was allowed to proceed at room temperature overnight. The filtered solution was evaporated to dryness *in vacuo* and the residue was dissolved in

[3]*All melting points are uncorrected. Microanalyses were performed by Micro Tech Laboratories, Skokie, Illinois.*

chloroform. The chloroform solution was extracted with water, dried, and then evaporated to dryness. The residue on treatment with benzene gave 3.7 g. (25%) of crude crystalline 1,3-di-(carbomethoxymethyl) thiourea (m.p. 97°–98° C.). Several crystallizations from benzene–hexane solution gave colorless platelets melting at 99°–100° C. Anal. Calc. for $C_7H_{12}N_2O_4S$: C, 38.17; H, 5.49; N, 12.72; S, 14.56%. Found: C, 38.59; H, 5.61; N, 12.81; S, 14.10%.

Part of the 1,3-di-(carbomethoxymethyl) thiourea (0.5 g., 0.002 mole) in a solution of sodium hydroxide (0.3 g., 0.007 mole) in water (7 ml.) was heated on a steam bath for 30 minutes. The solution was cooled to 0° C. and acidified with cold concentrated hydrochloric acid solution. The crystals (m.p. 157°–158° C.; resolidifies and remelts with decomposition at 214°–215° C.) were recovered by filtration, yield 0.38 g. (89%). This material was purified by solution in cold methanol and precipitation with benzene. The pure sample gave a double melting point of 164°–165° C. and 214°–215° C. with decomposition. Anal. Calc. for $C_5H_8N_2O_4S$: C, 31.25; H, 4.20; N, 14.58; S, 16.69%. Found: C, 31.49; H, 4.23; N, 14.43; S, 16.61%.

The mother liquors and washings from the preparation of 1,3-di-(carbomethoxymethyl) thiourea were combined and evaporated to dryness. The residue in concentrated hydrochloric acid solution (35 ml.) was warmed on a steam bath for 20 minutes. When the solution was cooled, 2-thio-3-(carboxymethyl) hydantoin (m.p. 210°–212° C. with decomposition) separated as pale yellow crystals, yield 2 g. (17%). Recrystallization from methanol–benzene solution raised the melting point to 214°–215° C. with decomposition. The melting points reported in the literature are 212° C. with decomposition (4) and 210°–212° C. (5). Anal. Calc. for $C_5H_6N_2O_3S$: C, 34.47; H, 3.47; N, 16.09; S, 18.41%. Found: C, 34.55; H, 3.54; N, 16.10; S, 18.21%.

A solution of 2-thio-3-(carboxymethyl) hydantoin (0.5 g., 0.003 mole) in 10% methanolic hydrogen chloride solution (10 ml.) was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* at room temperature and the crystalline residue was crystallized from benzene (3 ml.) to yield 0.49 g. (91%) of 2-thio-3-(carbomethoxymethyl) hydantoin melting at 112°–113° C. One crystallization from benzene–hexane solution raised the melting point to a constant value of 113°–114° C. Anal. Calc. for $C_6H_8N_2O_3S$: C, 38.29; H, 4.28; N, 14.89; S, 17.04%. Found: C, 38.51; H, 4.37; N, 14.46; S, 16.74%.

The methyl ester of 2-thio-3-(carboxymethyl) hydantoin on hydrolysis with either 6% potassium hydroxide solution or 37% hydrochloric acid solution gave a 72% yield of 2-thio-3-(carboxymethyl) hydantoin (m.p. 214°–215° C. with decomposition). The product was identified by a mixture melting point determination with an authentic sample of 2-thio-3-(carboxymethyl) hydantoin.

The second portion of solution from the original reaction was acidified to a pH of 2 with concentrated hydrochloric acid solution. This solution was evaporated to dryness *in vacuo* and the residue was dried *in vacuo* over potassium hydroxide pellets. The dried residue was extracted with boiling methanol (2×100 ml.) and the insoluble inorganic salts were removed by filtration. After the methanolic filtrate was taken to dryness, the residue was crystallized from water (15 ml.). Orange-red crystals of condensation product (m.p. 270°–275° C. with decomposition) were obtained, yield 2.9 g. (24%). One crystallization from water (7 ml.) together with treatment with Nuchar raised the melting point to 287°–290° C. with decomposition. The product gave a negative halogen test and it gave a neutralization equivalent of 373 on titration with 0.1 *N* sodium hydroxide solution. Anal. Calc. for $C_{10}H_8N_4O_6S_2Na_2$ (mol. wt. 374.31): C, 32.09; H, 2.15; N, 14.97%. Found: C, 32.50; H, 3.13; N, 15.11; Ash, 17.53%.

The mother liquors from the condensation product were evaporated to dryness and the residue was heated with 37% hydrochloric acid solution (25 ml.) for 1 hour on the steam bath. The solution was cooled and a crystalline precipitate of 2-thio-3-(carboxymethyl) hydantoin (m.p. 210°–212° C. with decomposition) was obtained, yield 2.6 g. (23%). This product was identified by a mixed melting point determination with a known sample of 2-thio-3-(carboxymethyl) hydantoin (m.p. 214°–215° C. with decomposition).

In another experiment, after the stage of the condensation reaction, the reaction mixture was acidified with 1.1 mole of hydrochloric acid per mole of sodium hydroxide originally used. The colored condensation product (m.p. 285°–290° C. with decomposition) was obtained in 32% yield. The dry residue from the mother liquors was methylated with 10% methanolic hydrogen chloride to yield 7% of the methyl ester of 2-thio-3-(carboxymethyl) hydantoin (m.p. 112°–113° C.). This product gave no depression in melting point on admixture with an authentic sample of 2-thio-3-(carbomethoxymethyl) hydantoin (m.p. 113°–114° C.).

Direct Preparation of 2-Thio-3-(carboxymethyl) Hydantoin

A mixture of glycine (150 g., 2 moles), carbon disulphide (76 g., 1 mole), and sodium hydroxide (80 g., 2 moles) in water (350 ml.) was condensed in the above-described manner. After complete reaction, the solution was filtered and evaporated to dryness. The residue in concentrated hydrochloric acid solution (500 ml.) was heated on a steam bath for 45 minutes. The yellow solid which separated was collected and dried to give 84 g. (49%) of 2-thio-3-(carboxymethyl) hydantoin (m.p. 214°–215° C. with decomposition). This product was identified by a mixture melting point determination.

3-(Carboxymethyl) Hydantoin

2-Thio-3-(carboxymethyl) hydantoin (1.3 g., 0.007 mole) was converted into 3-(carboxymethyl) hydantoin (m.p. 183°–191° C.) in 37% yield by heating with chloroacetic acid under the conditions described by Johnson and Renfrew (5). Two crystallizations from ethanol–hexane solution raised the melting point to 197°–198° C. The melting points reported in the literature are 190°–191° C. (5), 195°–196° C. (16), and 199°–201° C. (17). Anal. Calc. for $C_5H_6N_2O_4$: C, 37.98; H, 3.83; N, 17.72%. Found: C, 38.28; H, 3.94; N, 17.95%.

A solution of 3-(carboxymethyl) hydantoin (0.1 g., 0.0006 mole) in 10% methanolic hydrogen chloride solution (8 ml.) was allowed to stand overnight. The solvent was removed *in vacuo* and the residue was crystallized from benzene–hexane solution to give 91 mg. (84%) of the methyl ester of 3-(carboxymethyl) hydantoin melting at 88°–89° C. One crystallization from acetone–hexane solution raised the melting point to 90°–91° C. The previously (3) reported melting point is 91° C.

Chemistry of the Condensation Product

(*a*) *Conversion into 2-Thio-3-(carboxymethyl) Hydantoin*

The condensation product (0.5 g., 0.0013 mole) in 37% hydrochloric acid solution (4 ml.) was heated at 100° C. for 7 minutes. The mixture was cooled and the precipitate of 2-thio-3-(carboxymethyl) hydantoin (m.p. 212°–213° C. with decomposition) was removed by filtration, yield 0.39 g. (84%). One crystallization from glacial acetic acid raised the melting point to 214°–215° C. with decomposition. This product was identified by a mixture melting point determination with a known sample of 2-thio-3-(carboxymethyl) hydantoin.

(*b*) *Conversion into 2-Thio-3-(carbomethoxymethyl) Hydantoin*

A solution of the condensation product (0.5 g., 0.0013 mole) in 10% methanolic hydrogen chloride solution (10 ml.) was allowed to stand at room temperature overnight. The solvent was removed *in vacuo* and the residue was extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated to dryness. The crystalline residue was crystallized from benzene, yield 0.4 g. (81%). It melted at 112°–113.5° C. alone and on admixture with a known sample of 2-thio-3-(carbomethoxymethyl) hydantoin (m.p. 113°–114° C.).

(*c*) *Conversion into 3-(Carbomethoxymethyl) Hydantoin*

An aqueous solution (2 ml.) of the condensation product (0.5 g., 0.0013 mole) and chloroacetic acid (0.5 g., 0.005 mole) was refluxed for 1 hour. The solution was taken to dryness *in vacuo* and the residue was methylated with 10% methanolic hydrogen chloride solution (15 ml.) at room temperature overnight. The solvent was removed *in vacuo* and the residual oil was dissolved in chloroform. The chloroform solution was washed with 5% sodium bicarbonate solution and water. It was dried and the chloroform evaporated. The residue was crystallized from benzene–hexane solution (3 ml.) to give 116 mg. (25%) of 3-(carbomethoxymethyl) hydantoin melting at 89°–90° C. A sample crystallized from acetone–hexane solution melted at 90°–91° C. alone and on admixture with a known sample of 3-(carbomethoxymethyl) hydantoin.

(*d*) *Condensation Product from 2-Thio-3-(carboxymethyl) Hydantoin*

A solution of 2-thio-3-(carboxymethyl) hydantoin (5.0 g., 0.0287 mole) in water (100 ml.) was titrated with 0.1 *N* sodium hydroxide solution. After each addition of base, the pH of the solution was determined by means of a Beckman Model G pH meter equipped with external glass and calomel electrodes. At the neutralization point (288 ml. of 0.1 *N* NaOH, 0.0288 mole), the color of the solution changed from pale yellow to red. After addition of an equal amount of base, the solution was back-titrated with 118 ml. of 0.244 *N* hydrochloric acid (0.0288 mole). Again, a color change from red to orange at the equivalence point was observed when approximately half of the hydrochloric acid solution had been added. The solution was evaporated *in vacuo* until crystals began to appear. These were collected and dried to give 1.28 g. (m.p. 287°–292° C. with decomposition). A second crop (3.02 g., m.p. 270°–285° C. with decomposition) was obtained on further concentration of the mother liquor to give a total crude yield of 80%. Recrystallization of the product from water (10 ml.) together with Nuchar treatment gave orange-red crystals (2.04 g., m.p. 287°–291° C. with decomposition) which gave no depression in melting point on admixture with the condensation product (above). It gave a neutralization equivalent of 378 on titration with 0.1 *N* sodium hydroxide solution. Anal. Calc. for $C_{10}H_8N_4O_5S_2Na_2$: C, 32.09; H, 2.15; N, 14.97%. Found: C, 32.61; H, 3.36; N, 15.55; Ash, 17.47%.

(*e*) *Titration Experiments*

The titration curves (Fig. 1 and 2) were obtained by titration of aqueous solutions (1 g./100 ml.) of 2-thio-3-(carboxymethyl) hydantoin and the condensation product with 0.1 *N* sodium hydroxide solution and back-titration with standardized hydrochloric acid solution. The pH of the solution was determined by means of a Beckman Model G pH meter equipped with external glass and calomel electrodes.

1,3-Di-(β-carboxyethyl) Thiourea

A mechanically stirred mixture of β-alanine (15 g., 0.16 mole), carbon disulphide (6.4 g., 0.08 mole), and water (10 ml.) was treated dropwise with a solution of sodium

hydroxide (6.7 g., 0.17 mole) in water (17 ml.) over a period of 5 minutes. The temperature gradually rose to 30° C. and in 30 minutes all of the carbon disulphide had been consumed in the reaction. Additional carbon disulphide (2 g.) was added and the solution was heated at the reflux temperature for 30 minutes. The excess carbon disulphide was removed by distillation and the clear solution was refluxed for 7 hours. It was cooled and then filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 2 with 10% hydrochloric acid solution and then evaporated to dryness *in vacuo*. The residue was extracted with hot methanol to remove the inorganic salts. The dry residue from the methanolic extract was treated with 5% methanolic hydrogen chloride solution (50 ml.) and allowed to stand at room temperature overnight. The residue from evaporation of the methanolic solution was dissolved in chloroform and the chloroform solution was washed with 5% hydrochloric acid solution, 5% sodium bicarbonate solution, and water. The dried chloroform solution was evaporated to dryness *in vacuo* and the residue was crystallized from cold benzene (60 ml.), yield 11.6 g. (56%). The melting point was raised from 69°–73° C. to 73°–74° C. by one crystallization from methanol–water solution, yield 10.4 g. Anal. Calc. for $C_9H_{16}N_2O_4S$: C, 43.53; H, 6.50; N, 11.28; S, 12.92%. Found: C, 43.93; H, 6.65; N, 11.10; S, 12.65%.

The dimethyl ester of 1,3-di-(β-carboxyethyl) thiourea (5.5 g., 0.02 mole) in a solution of potassium hydroxide (3.7 g.) in water (65 ml.) was heated on a steam bath for 45 minutes. The solution was cooled, acidified to pH 2 with 10% sulphuric acid solution, and then evaporated to dryness. The residue was extracted with acetone (2×100 ml.). After the acetone was evaporated from the combined extracts, the residue was crystallized from acetone–chloroform solution. This procedure gave 4.5 g. (93%) of 1,3-di-(β-carboxyethyl) thiourea melting at 137°–139° C. A further crystallization from the same solvent pair raised the melting point to 138°–139° C. Anal. Calc. for $C_7H_{12}N_2O_4S$: C, 38.18; H, 5.50; N, 12.73; S, 14.56%. Found: C, 38.18; H, 5.66; N, 12.45; S, 14.68%.

1,3-Di-(β-carboxyethyl) Urea

Method A

A solution of 1,3-di-(β-carboxyethyl) thiourea (1.4 g., 0.006 mole) and sodium hydroxide (1.1 g., 0.028 mole) in water (10 ml.) was treated at 20°–25° C. with 32 ml. (0.028 mole) of 0.891 *M* sodium hypochlorite solution. The addition was complete in 5 minutes and the oxidation was allowed to proceed at room temperature overnight. A small amount of insoluble sulphur was removed by filtration, and the filtrate was acidified with 10% hydrochloric acid to pH 2. It was evaporated *in vacuo* on the steam bath to a volume of 20 ml. or until white crystals began to appear. The solution was cooled and the crystals were collected, washed, and dried, yield 1.07 g. (80%). The melting point was raised from 183°–185° C. to 185°–185.5° C. by crystallization from methanol. Anal. Calc. for $C_7H_{12}N_2O_5$: C, 41.17; H, 5.93; N, 13.72%. Found: C, 41.17; H, 5.98; N, 13.68%.

Method B

A mixture of the dimethyl ester of 1,3-di-(β-carboxyethyl) thiourea (10 g., 0.04 mole) and sodium hydroxide (6.4 g., 0.16 mole) in water (70 ml.) was dissolved by slight warming on a steam bath. The solution was cooled and treated with 7.9 *M* hydrogen peroxide solution (20.4 ml., 0.16 mole) at 15°–20° C. The oxidation was allowed to proceed at room temperature overnight, after which the pH of the solution was adjusted to 2 with 37% hydrochloric acid solution. This solution was concentrated *in vacuo* until crystals began to appear. The crystals (m.p. 183°–185° C.) were removed by filtration and dried, yield 7.1 g. (86%). These crystals did not depress the melting point of 1,3-di-(β-carboxyethyl) urea (m.p. 185°–185.5° C.) prepared by Method A.

2-Thio-3-(β-carboxyethyl) Hydrouracil

β-Alanine (75 g., 0.8 mole) and carbon disulphide (35 g., 0.46 mole) in a solution of sodium hydroxide (33.7 g., 0.8 mole) in water (135 ml.) were condensed in the usual manner by refluxing for 7 hours. This solution was cooled, acidified to a pH of 2 with concentrated hydrochloric acid, and evaporated to dryness. The residue was extracted with hot methanol and the methanol extract was taken to dryness *in vacuo*. The residual oil was heated with *p*-toluenesulphonic acid monohydrate (8 g.) at 160°–175° C. *in vacuo* (15 mm.) for 30 minutes. This melt on crystallization from water (200 ml.) gave 38.8 g. (46%) of 2-thio-3-(β-carboxyethyl) hydrouracil (m.p. 163.5°–164.5° C.). Crystallization from acetone–water solution raised the melting point to 166°–167° C. Anal. Calc. for $C_7H_{10}N_2O_3S$: C, 41.57; H, 4.98; N, 13.86; S, 15.86%. Found: C, 41.80; H, 4.89; N, 14.00; S, 15.90%.

In another experiment a mixture of 1,3-di-(β-carboxyethyl) thiourea (0.5 g., 0.002 mole) and *p*-toluenesulphonic acid monohydrate (0.05 g., 0.0003 mole) was heated at 160°–175° C. for 10 minutes. The melt was cooled and crystallized from water (4 ml.) to give 0.4 g. (85%) of 2-thio-3-(β-carboxyethyl) hydrouracil melting at 166°–167° C.

2-Thio-3-(β-carboxyethyl) hydrouracil (0.5 g., 0.002 mole) was heated on a steam bath for 35 minutes in a solution of 85% potassium hydroxide (0.48 g., 0.007 mole) in water (8 ml.). This solution on acidification to pH 2 and evaporation to a small volume gave 1,3-di-(β-carboxyethyl) thiourea (m.p. 137°–138° C.) in 75% (0.41 g.) yield. The product was identified by a mixture melting point determination.

3-(β-Carboxyethyl) Hydrouracil

Method A

A mixture of 1,3-di-(β-carboxyethyl) urea (1 g., 0.005 mole) and acetic anhydride (10 ml.) was refluxed for 15 minutes. The solution was cooled, diluted with 100 ml. of water, and the excess acetic anhydride allowed to hydrolyze. Evaporation of the aqueous solution *in vacuo* on the steam bath gave a crystalline residue. The residue was crystallized from ethanol–benzene solution (10 ml.) to yield 0.59 g. of product. Concentration of the mother liquors gave another 0.1 g. of crystalline product. The total yield of 3-(β-carboxyethyl) hydrouracil (m.p. 178°–184° C.) was 76%. One crystallization raised the melting point to 183°–184° C. A sample of this compound mixed with the starting material, 1,3-di-(β-carboxyethyl) urea (m.p. 185°–185.5° C.), gave a depressed melting point. Anal. Calc. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.41; N, 15.05%. Found: C, 45.50; H, 5.48; N, 15.23%.

Method B

A solution of 1,3-di-(β-carboxyethyl) urea (0.5 g., 0.0025 mole) in 37% hydrochloric acid solution (3 ml.) was evaporated to dryness in an open beaker on a steam bath. This procedure was repeated twice and the final dry residue was extracted with hot acetone (25 ml.). After the solvent was removed by evaporation, the residue was crystallized from acetone–chloroform solution. The crystals melted at 172°–175° C., yield 0.38 g. (83%). One crystallization from methanol–benzene solution raised the melting point to 181°–182° C. A mixture melting point determination with a known sample of 3-(β-carboxyethyl) hydrouracil gave no depression.

Method C

1,3-Di-(β-carboxyethyl) thiourea (0.27 g., 0.001 mole) in acetic anhydride (5 ml.) was refluxed for 30 minutes. The solution was cooled, poured into ice-water (25 ml.), and the excess acetic anhydride was allowed to hydrolyze at room temperature. The oil remaining after evaporation of the solution was crystallized from acetone–chloroform solution. The

crude crystalline product (m.p. 179°–181° C.) was obtained in 26% (0.059 g.) yield. After two recrystallizations from the same solvent pair it melted at 183°–184° C. alone and on admixture with a known sample of 3-(β-carboxyethyl) hydrouracil (m.p. 183°–184° C.).

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PHOTOCONDUCTIVITY AND ABSORPTION AND FLUORESCENCE SPECTRA OF 9,10-DICHLOROANTHRACENE[1]

E. BOCK,[2] J. FERGUSON,[3] AND W. G. SCHNEIDER

ABSTRACT

The spectral response, voltage, light intensity, and temperature dependences of the photocurrent generated in crystals of 9,10-dichloroanthracene have been studied as well as the absorption and fluorescence spectra. The magnitude of the measured photocurrent was 10^2–10^3 times larger than that observed in anthracene under similar conditions. The spectral response of the photocurrent in the surface cell arrangement was found to depend on the direction of the incident light relative to the electrodes. Above a certain value of the applied voltage the photocurrent was found to be ohmic. The photocurrent increased as the 0.7 or 0.8 power of the light intensity depending on whether the light was incident on the same side or opposite sides of the crystal face containing the electrodes. When the crystal was cooled the photocurrent passed through a maximum between 20° and 0° C.

The absorption edge of crystalline 9,10-dichloroanthracene as well as the absorption spectrum in chloroform solution were determined. When the crystals were cooled the fluorescence spectrum was observed to shift to longer wavelengths and the intensity increased between two and three times.

INTRODUCTION

Compton and Waddington (1) observed that anthracene crystals treated with either NO_2 or Cl_2 gas showed marked and permanent changes in the photoconduction. They attributed the changes to the formation of complexes between the anthracene and the gases. In the case of Cl_2 there is the possibility of the formation of 9,10-dichloroanthracene under the conditions of their experiments, and it was therefore decided to investigate the photoconduction of this substance in the pure crystalline state. Furthermore, 9,10-dichloroanthracene is an interesting compound in its own right since the presence of the heavy atoms should facilitate internal conversion from singlet to triplet states. The fact that the photocurrents observed were 10^2–10^3 times those usually encountered in anthracene under similar conditions suggests that this mechanism may have some importance, although it is of course not necessarily the determining factor giving rise to the enhanced photoconduction in the present case.

EXPERIMENTAL

Reagent grade 9,10-dichloroanthracene, obtained from Eastman Organic Chemicals, was purified by chromatography through alumina and was then recrystallized from light petroleum.

The crystals were grown from carbon tetrachloride solution as this solvent was found to produce the best crystals. Typical dimensions were: 1×0.2 cm. and $50 \pm 20\ \mu$ thick. Attempts at growing crystals by sublimation resulted in very thin needles, too fragile for handling.

X-Ray measurements showed the crystals to belong to the orthorhombic system and it was established that most, if not all, of the crystals were multiple twins. The most-developed plane was the (010) face, which is also the twinning plane. The electrodes (colloidal suspension of graphite in alcohol) were both placed on this (010) face with a separation of between 0.6 and 0.8 mm. Electrodes were considered "good" only when

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there was no apparent space charge associated with the photocurrent. The photocurrents were measured with a Keithley micromicroammeter and were of the order 10^{-7} to 10^{-11} amp. Since it was observed that air increased the photocurrent, all measurements were carried out in an inert atmosphere of argon. The temperature dependence of the photocurrent was measured with an almost identical arrangement to that of Kommandeur, Korinek, and Schneider (2). The absorption and fluorescence measurements were obtained with a semiautomatic Beckman DU spectrometer.

RESULTS AND DISCUSSION

A. Photoconduction

I. Photocurrent–Wavelength Relation

Fig. 1 shows that the spectral dependence for a surface cell is sensitive to the direction of the incident light. When the electrodes are carefully placed only on one (010) face of the crystal the spectral dependence with the light incident normal to this face is different to the case when the light is incident normal to the opposite (010) face of the crystal. Anthracene sublimation flakes have also been observed to show a variation of the spectral dependence with a surface cell arrangement when the direction of the incident light is changed (3), and this behavior, hitherto unnoticed, may well be quite general and should be looked for in all surface cell measurements.

Fig. 1 also shows the absorption edge of a typical crystal in polarized light. Spectral dependences were determined with polarized light but the differences between the two polarizations are not great and the curves in Fig. 1 are therefore for unpolarized light.

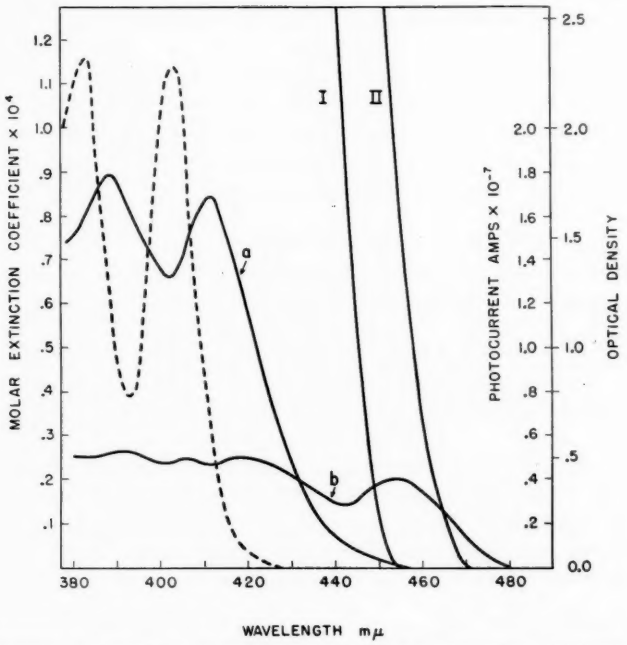

FIG. 1. Broken curve, molar extinction coefficient in $CHCl_3$. *a*, photocurrent with front face illuminated; *b*, photocurrent with back face illuminated. I and II, optical density of crystal: I, light polarized parallel to *c* axis; II, light polarized parallel to *a* axis.

When the light is incident normal to the face on which the electrodes are placed the photocurrent response curve shows two maxima, at 3875 and 4135 Å. Essentially the same spectral dependence was obtained with a total of six crystals. If the spectral dependence is compared with the absorption edge it will be seen that the maximum photocurrent is obtained only at wavelengths well below those corresponding to absorption edge optical densities of 2.0 (99% light absorbed), i.e., at 4415 and 4530 Å. However, if the light is incident on the opposite (010) face of the crystal a marked change is found in the spectral dependence. Only one peak is observed, at 4525 Å, and the response at lower wavelengths is relatively uniform. The peak appears slightly displaced to the long-wavelength side of the absorption edge. Unfortunately the crystals were far too thick to permit the determination of the complete absorption spectrum, and lacking this we cannot say whether there is any relation between the spectral dependence and the absorption spectrum for either of the two arrangements. It is however only in the *latter* arrangement, with the back crystal face illuminated, that the photocurrent reaches a maximum in the vicinity of the absorption edge.

II. Photocurrent – Light Intensity Relation

The photocurrent was found to be proportional to the 0.7 power of the light intensity when the light was incident normal to the face with the electrodes. With the light incident normal to the opposite face the relation involved the 0.8 power of the light intensity. This behavior was found over the whole spectral region from 3800 to 4700 Å, and typical results are shown in Fig. 2.

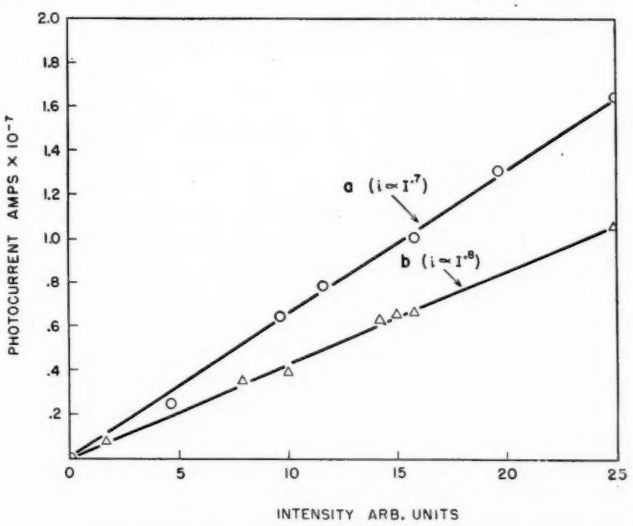

FIG. 2. Light intensity – photocurrent relation: *a*, front face illuminated; *b*, back face illuminated.

The increase of the photocurrent as a fractional power of the light intensity means that the carrier lifetime is shortened when the light intensity is increased (4), presumably by some recombination process.

III. Photocurrent–Voltage Relation

The voltage dependence was determined over the spectral region 3800 to 4700 Å. It was found to increase slowly (see Fig. 3) at low field strengths up to a value, different

for each crystal, of about 350±100 v./cm.; above this point the photocurrent increased linearly with applied voltage. This behavior, which was similar when either the front or back crystal face was illuminated, was observed with all crystals measured. No saturation or deviation from linearity was found for the highest field strengths used, about 5000 v./cm.

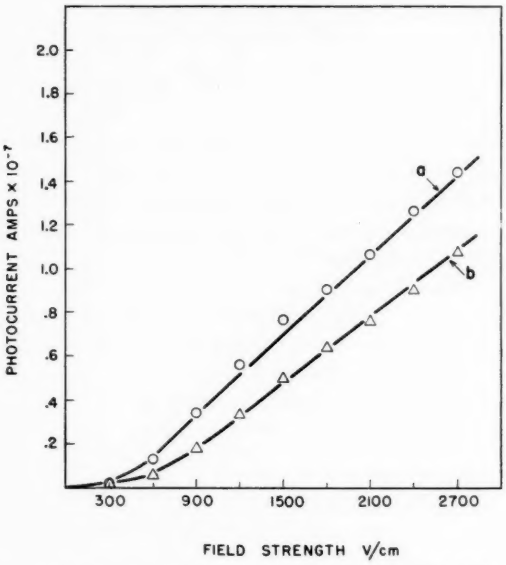

FIG. 3. Voltage–photocurrent relation: *a*, front face illuminated; *b*, back face illuminated.

IV. Photocurrent–Temperature Relation

Kommandeur, Korinek, and Schneider (2) studied the temperature dependence of the photocurrents from a number of organic crystals and they found that the photocurrents decrease exponentially with decreasing temperature. However, when 9,10-dichloroanthracene was cooled the photocurrent was observed to pass through a maximum between 20° and 0° C. On further cooling the photocurrent decreased, but as the crystals are very sensitive to thermal shock this could not be followed accurately. A similar behavior, but at higher temperature, was found by Drefahl and Henkel (5) with 4,4′-diphenylstilbene. This behavior may be related to the increase in the fluorescence efficiency that was found when the crystals were cooled (see below). This observation then supports a growing body of evidence that any process which quenches the electronic excitation energy of a crystal, whether it be energy transfer to an impurity or thermal-induced lattice quenching, leads to a decrease of the photocurrent.

B. Absorption and Fluorescence

As mentioned above in connection with the spectral dependence, all of the crystals were far too thick to penetrate the absorption band so only the absorption edge could be measured. From Fig. 1 it can be seen that this edge is at much longer wavelengths than the absorption band in solution so that intermolecular interactions are considerable.

The number of molecules in the unit cell is uncertain but from what is known about the crystal structure it seems likely that the molecules are stacked with the molecular

planes more nearly parallel to the *ab* crystal plane than any other. In addition, the short axis of the anthracene framework lies most likely closer to the *b* crystal axis than the other two. These considerations are in agreement with visual observations of the polarization of the fluorescence emitted normal to the (010) and (100) faces at room temperature, if the molecular transition is polarized along the short molecular axis. These observations are that normal to the (100) plane the fluorescence is strongly polarized parallel to the *b* crystal axis, while normal to the (010) plane the fluorescence is greater along the *a* crystal axis than along the *c*, but the ratio is not as high as in the former case.

The fluorescence spectra reported here were taken normal to the (010) face as this is the most developed. The striking feature of the fluorescence spectrum is that at room temperature the origin lies well inside the absorption edge. This is found only when the fluorescence is observed from the face which is irradiated. When the crystal is cooled the fluorescence spectrum is shifted to longer wavelengths and the relative intensities of individual bands is altered, but the total intensity of emission is increased. These changes are shown in Fig. 4, which records the *a* polarized component (the *c* component is similar

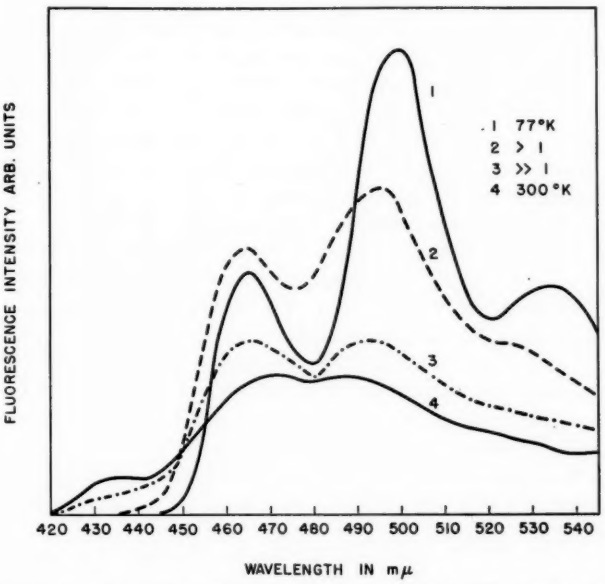

FIG. 4. Fluorescence spectrum at various temperatures: (1) 77° K., (2) >77° K., (3) ≫77° K., (4) room temp. ~290° K.

but weaker by a factor between 3 and 4) at room temperature, 77° K., and two intermediate temperatures. These spectra were all taken without moving the sample or the optical arrangement. All of the crystals examined showed the same fluorescence spectrum at 77° K. and measurements with two crystals at 4° K. produced very little further sharpening of the bands.

We are greatly indebted to Dr. M. Przybylska for crystallographic examinations of 9,10-dichloroanthracene.

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THE CHANGE OF PHOTOCONDUCTION AND SEMICONDUCTION IN AROMATIC HYDROCARBONS ON MELTING[1]

J. KOMMANDEUR,[2] G. J. KORINEK,[3] AND W. G. SCHNEIDER

ABSTRACT

The variation of the photocurrent and dark current on melting naphthalene and biphenyl was studied. A large increase in the value of the photocurrent was observed. This change is very similar to that of the dark current. It is concluded that the increased mobilities of the charge carriers in the melt are mainly responsible for the change in both cases. The existence of photoconduction in the non-crystalline state is discussed.

INTRODUCTION

The investigation of various aspects of the photoconductivity of aromatic hydrocarbons has been reported from this laboratory (1, 2, 3). The present communication deals with the changes of the photo- and semi-conduction connected with the transition from crystal to melt.

It was observed earlier by Riehl (4) and Rabinowitch (5) that the semiconductivity of anthracene, paraffin, and naphthalene increases by a factor up to 10^3–10^4 on melting. The change is largest with pure material and single crystals and is less with the increasing amount of impurities or in polycrystalline material. This may explain why some of the earlier investigators (6) did not observe this change.

The large increase in semiconductivity of anthracene, paraffin, and naphthalene on melting is similar to that of ionic conductors. The observed ratio of σ_L, the conductivity of the liquid, to σ_S, that of the solid, is anywhere between 10 and 10^5. This change in conductivity is associated in ionic substances with the large increase in the number of lattice flaws on melting and with the fact that the expansion in volume on fusion reduces the activation energy for migration of the ions.

In contrast with ionic conductors, in metals there is a decrease in conductivity on melting, this being the result of increased scattering of electrons in the molten metal owing to the greater disorder of the atoms.

It was of interest to study the influence of melting on photoconduction, the result of which could possibly contribute to the elucidation of its mechanism. Naphthalene and diphenyl were the substances studied. Both photoconduct, are obtainable as single crystals, and have reasonably low melting points. This condition is of great importance because the semiconduction increases much faster with temperature than the photoconduction and the higher the melting point the greater is the dark current, which may completely mask any change in photocurrent.

EXPERIMENTAL

Naphthalene and biphenyl used were purified by chromatography through alumina and subsequent recrystallization from petroleum ether. The purification was carried out in the dark.

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Single crystals were used exclusively. They were grown for us by Dr. F. R. Lipsett in a Bridgman furnace (7). Only those sections of the crystals which were free of flaws were used.

APCO-15 (colloidal graphite in alcohol, supplied by APCO Industries Limited) and silver paste (Hanovia Mfg. Co.) electrodes were used first. Both these electrodes proved unsatisfactory because during the melting they contaminated the melt and increased the semiconductivity by several orders of magnitude. The only arrangement which proved feasible was to carefully melt the crystal at its edges; the melt wetted the platinum electrodes and established the contact.

Because of the known effect of gases on photoconduction all measurements were done on outgassed single crystals in vacuum ($\sim 10^{-5}$ mm. Hg).

The measurements were carried out in a properly shielded glass silica cell (see Fig. 1). The cell was designed in such a way that the field strength was practically the same for

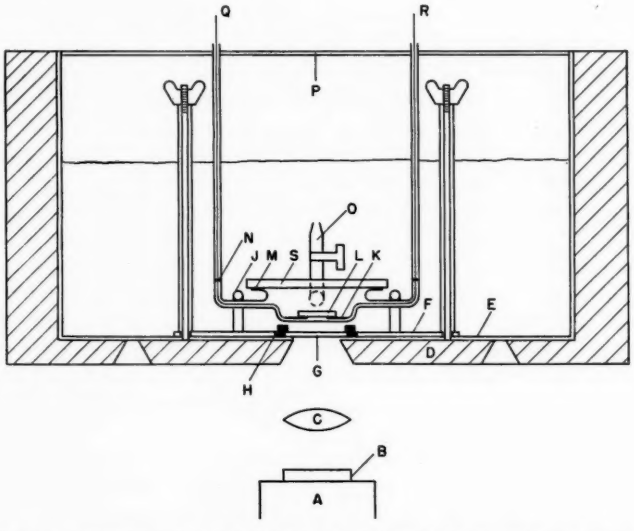

FIG. 1. Cell for the measurement of the change of semi- and photo-conduction on melting a single crystal.

A—Mercury lamp
B—Filter
C—Lens
D—Insulation
E—Brass
F—Removable carriage
G—Silica window
H—Seal
J—Clamps
K—Pt electrodes
L—Crystal
M—Ground joint
N—Kovar seal
O—Connection to vacuum
P—Cover
Q—Battery connection
R—Connection to Keithley
S—Glass cover

single crystals and the melt. Measurements were taken in the direction of increasing temperature and at temperatures ranging from 290° to 373° K., which include the melting point. The procedure could of course not be reversed, since once the single crystal was melted, subsequent cooling results in a polycrystalline mass.

The cell was mounted on a brass carriage which could at any time be removed or submerged in the water bath. This mounting provided the greatest stability and avoidance of vibrations.

The currents were measured with a Keithley micromicroammeter as described earlier

(3). In the cases where the photocurrent was substantially smaller than the dark current, the latter was "bucked out" by applying an auxiliary e.m.f. from a battery circuit. The ultraviolet light source employed was a BTH direct-current 250 w. mercury lamp, operated from a stabilized (Nobatron) d-c. power source. A filter cutting off all wavelengths shorter than 3000 Å was used.

RESULTS

Fig. 2 shows a plot of the log of the photocurrent vs. $1/T$ for naphthalene. The plot is a fairly straight line until just below the melting point, where a curvature appears. At the melting point there is a sharp rise in the photoconduction by a factor of 10^3. The graph is very similar to Fig. 3, which depicts the dependence of the semiconductivity of naphthalene on temperature. Three crystals of naphthalene yielded results similar to those shown on Figs. 2 and 3.

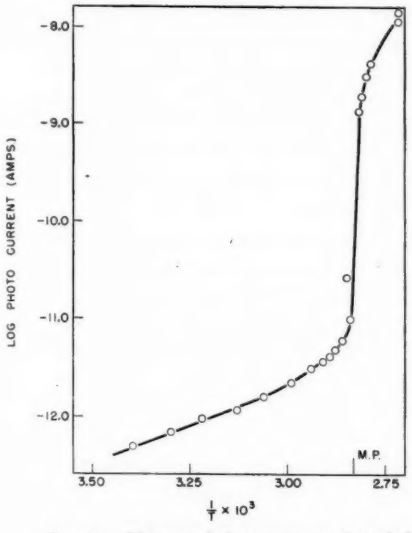

FIG. 2. Change of photocurrent of naphthalene upon melting.

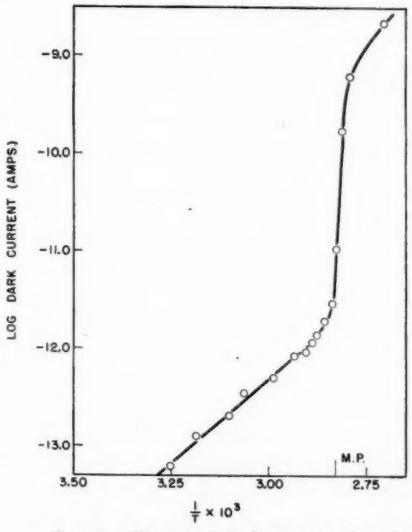

FIG. 3. Change of dark current of naphthalene upon melting.

Figs. 4 and 5 show the dependence of photo- and semi-conduction on temperature for diphenyl. In this case the log of photocurrent vs. $1/T$ dependence is hardly linear even in the intermediate region. The curvature is more pronounced and the rise at the melting point is only about a factor of 10. The logarithm of the dark current vs. the inverse temperature yields a good straight line nearly to the melting point and then a sharp increase by a factor of 10^2. A similar behavior was observed on two other crystals of biphenyl. From the slopes of the dark current vs. $1/T$ plots from room temperature until just below the melting point activation energies were determined from the relation $i = i_0 e^{-E/RT}$. Their average values are 16.5 ± 1.0 kcal. for naphthalene and 16.7 ± 0.7 kcal. for biphenyl. The value for naphthalene is close to that found by Riehl (4). The temperature dependence of the semiconduction of biphenyl has not been reported previously.

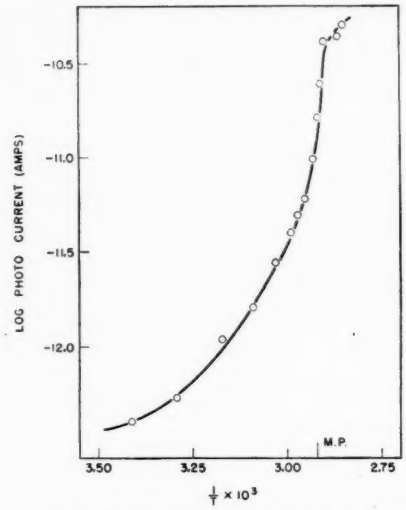

FIG. 4. Change of photocurrent of diphenyl upon melting.

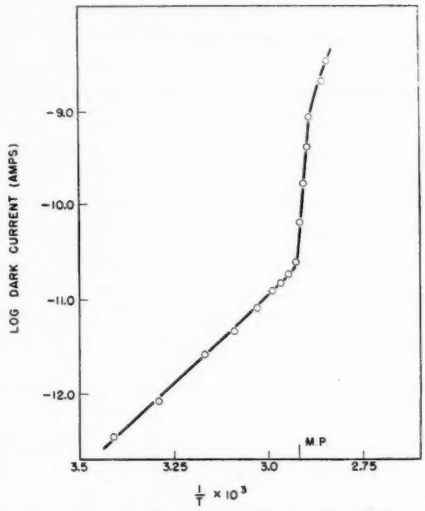

FIG. 5. Change of dark current of diphenyl upon melting.

DISCUSSION

As far as our understanding of the process of melting in the aromatic hydrocarbons goes, we can say that the melting is connected with some increase of positional disorder as evidenced, for example, by the increase in free volume. The fractional increase can be expressed as $f = (V_L - V_S)/V_S$, where V_L is the volume of melt per molecule at the melting point and V_S is the volume of solid per molecule at the melting point. It is of interest to note these values for naphthalene, biphenyl, and anthracene (8), which are: naphthalene, 16.7%; biphenyl, 12.4%; anthracene, 14.1%.

According to Riehl (9), the photoconduction of the solid at the melting point can be expressed by the equation $i_{solid} = CveFe^{-E/RT}$, where C is the concentration of the charge carriers, v the mobility, e the electronic charge, and F the applied field, and similarly in the melt $i_{melt} = C'v'eFe^{-E'/RT}$, where the symbols have the same meaning as above except that they apply to the melt.

Then in the case of naphthalene

$$\frac{i_{melt}}{i_{solid}} = 10^3 = \frac{C'v'eF}{CveF}\,\frac{e^{-E'/RT}}{e^{-E/RT}}.$$

The quantities which can change are C, v, and E.

The activation energy for the photoconductivity even in the crystal is very low, 2 kcal. (3), and was postulated to be connected with the transport process of the charge carriers through the crystal. Even if the value of the activation energy on going from crystal to the melt decreases to one-quarter of its value, it still cannot explain the large increase in photocurrent. Moreover, all the currents are seen to level off at higher temperatures, so there is no major permanent decrease in the activation energies. Riehl (9) showed that the activation energy for semiconduction undergoes no major change in going from the solid to the melt. Any increase in the activation energy of photoconduction will therefore also be limited. Thus $E \approx E'$.

The similarity of the changes of the photocurrent on melting with those of the dark current suggests that in both cases the pronounced change at the melting point has a common underlying cause. It is rather unlikely that the number of charge carriers would be changed by a very similar magnitude on melting irrespective of their being produced thermally as in semiconduction or optically as in photoconduction. Therefore $C = C'$. On the other hand, if on melting the transport of the charge carriers is facilitated, then it would be quite natural to expect a similar change in semiconduction and photoconduction on melting because for the transport process the way the charge carriers have been produced is of secondary importance. Thus $v' \gg v$.

The change in photocurrent as measured would involve any contribution to conductivity by movement of the molecular ions themselves which should be easier in the melt than in the solid. Nevertheless, this contribution should be rather small because (1) of the large size of molecular ions themselves (10); (2) at the melting point and at temperatures not too much above the melting point the melt is composed of clusters rather than of single molecules (8); (3) the activation energy for diffusion and migration of molecular ions should be substantially higher than that of electrons or positive holes.

We can conclude that even if there is a small contribution to the photocurrent in the melt due to the purely ionic conduction and due to the lowering of the activation energy of the charge carrier transport, the main contribution to the large increase of the photo- and semi-conductivity on melting must come from the change in the mobility of the charge carriers.

A further conclusion is that the photoconduction in aromatic hydrocarbons is not limited to the crystalline state. The existence of the photoconduction in the melt, as shown in this paper for naphthalene and biphenyl and also observed for stilbene by Henkel (11), and in a dispersion of anthracene in solid paraffin (down to concentration 2% by weight) (12) shows that an ordered arrangement of molecules in the lattice is not a necessary condition for photoconduction.

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THE SYSTEM LITHIUM NITRATE – ETHANOL – WATER AND ITS COMPONENT BINARY SYSTEMS[1]

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ABSTRACT

The system lithium nitrate – water has been investigated by thermal analysis and by X-ray powder diffraction studies. No trace of the hemihydrate reported by Donnan and Burt was found. The X-ray powder diffraction pattern of $LiNO_3.3H_2O$ has been obtained.

The equilibrium diagram of the system ethanol–water shows an inflection at −30° C., corresponding to 40 weight per cent ethanol. This is almost certainly a true peritectic point. The formula of the hydrate formed (if there is one) is uncertain but it may be $C_2H_5OH.5H_2O$.

The system lithium nitrate – ethanol could only be studied in dilute solution (of lithium nitrate) and at temperatures near room temperature, because of high viscosity and extreme supercooling. No evidence for the existence of a solid alcoholate has been obtained.

The system lithium nitrate – ethanol – water has been investigated in the form of a series of pseudobinary systems containing water and alcohol in fixed ratios. No solid alcoholate of lithium nitrate has been found in solutions containing less than 50 weight per cent ethanol. The investigation could not be pushed beyond this alcohol content because of high viscosity and supercooling.

INTRODUCTION

This study was undertaken as a result of work on the conductance of lithium nitrate in a mixed solvent of water and ethanol (1). We think that, as the alcohol content of such a solvent is increased, the solvation of the lithium ion must change, either progressively or suddenly, from a water solvation to an alcohol solvation, with consequent increase in the effective diameter of the lithium ion. We hoped to support this view by the isolation of a solid crystalline alcoholate of lithium nitrate, analogous to the water compound $LiNO_3.3H_2O$, but it appears, as a result of the work here described, that such an alcoholate does not exist, or at least that it cannot be isolated. Despite the failure of the original aim of this work, much interesting information has resulted, particularly that relating to the important system ethanol–water.

The system lithium nitrate – ethanol – water involves the three binary systems lithium nitrate – water, ethanol–water, and lithium nitrate – ethanol. The latter system has not previously been investigated but the first two have been the subjects of several researches.

The system $LiNO_3$–H_2O was first studied in detail by Donnan and Burt (2). They reported the existence of a congruently melting trihydrate and of a hemihydrate, which decomposed into anhydrous salt and solution at 61.1° C. Campbell and Kartzmark (3) repeated the dilatometric experiments of Donnan and Burt but were unable to find any evidence for the existence of the supposed hemihydrate; neither did hemihydrate appear in their isothermal study at 25° C.

The system ethanol–water has attracted the attention of many workers but much uncertainty has always surrounded it. This system is well known for its anomalous physical behavior, and the large deviations from ideality shown by its physical properties have often been put forward as evidence of compound formation. Maxima, minima, and discontinuities on curves of various physical properties versus concentration have led to the attribution of various formulae to supposed hydrates. A bibliography of the such physical properties as density, change in volume on mixing, and viscosity, as a function of composition of the homogeneous system, it cannot be accepted as evidence

[1]*Manuscript received September 9, 1957.*
Contribution from the Chemistry Department of the University of Manitoba, Winnipeg, Manitoba.
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in favor of compound formation. Anomalous physical properties can only indicate that interaction is taking place; they cannot give quantitative information about the nature of such interaction.

The soundest method of dealing with such problems is that of the phase rule and this has been applied as thermal analysis by several workers. The first systematic freezing-point determinations were carried out by Pictet (8) and by Pickering (9) but they were only interested in the point of first crystallization. Pushin and Glagoleva (10) made the first comprehensive thermal analysis and they concluded that no compounds are formed; they suggest, however, that solid solutions of ice in ethanol exist up to nearly 15 mole per cent water. Supercooling is a difficulty which has beset all investigators and this is particularly extensive in the region around 80 mole per cent ethanol.

Tarassenkov (11) repeated the thermal analysis measurements up to 75 weight per cent ethanol. He obtained an inflection on the freezing-point curve which he interpreted as evidence for the existence of a solid hydrate but he failed to obtain a peritectic halt on any cooling curve. The inflection fell at about 42 weight per cent ethanol and at $-33°$ C.

Shalberov and co-workers (12) have studied ethanol in solutions of concentration up to 53 mole per cent, as well as the ternary system ethanol – water – lithium chloride. In both systems they found a point of inflection which, for ethanol and water, fell at 34 weight per cent ethanol. Again, no peritectic halt was obtained. They suggest that the supposed hydrate has the formula $C_2H_5OH.5H_2O$.

Ross (13) determined the freezing points of a number of ethanol–water mixtures. He also obtained an inflection on the freezing-point curve at $-30°$ C. and 42 weight per cent ethanol.

The strongest indication of compound formation in the system ethanol–water is the occurrence of the point of inflection or break in the freezing-point curve but even this, without the presence of a peritectic halt on the cooling curve, cannot be accepted as truly significant unless there is further evidence that a second solid phase separates beyond this point. If this is a true peritectic point, the failure to obtain a peritectic halt is difficult to explain but the reason may lie in the persistent supercooling of alcohol–water mixtures: the peritectic halt may be hidden by the metastability of the system.

Studies of liquid ethanol at low temperatures throw some light on the physical anomalies and metastability of the system ethanol–water. Concentrated alcohol solutions supercool readily and eventually form a rigid glass near $-190°$ C. Prietzschk (14) studied the X-ray scattering at $-150°$ C. and at $-75°$ C. of liquid ethanol. From Fourier analysis he derived a radial intensity distribution curve of the pattern and from this he was able to deduce an average distribution of atoms. The structure thus determined is applicable to cold absolute alcohol and to cold alcohol containing a few per cent of water, and may be expected to give a qualitative indication of the interactions in any alcohol solution. At $-150°$ C., every oxygen atom is linked to two others, presumably by hydrogen bonding. We thus have a structure where the oxygen atoms are linked through hydrogen to form zigzag chains, the C_2H_5 groups lying at right angles to this chain. (Fig. 1 is a plane projection of such a three-dimensional chain.)

Harvey's investigation (15) of ethanol at $-75°$ C. gave the same result as that of Prietzschk. The number of nearest neighbors of each oxygen atom is found to be only older work (4, 5, 6, 7) is given but since all such work consists in the investigation of 1.2 at this temperature. This shows that the hydrogen bonding is becoming less as the temperature increases, but it is still quite appreciable at $-75°$ C.

Perfectly dry ethanol is readily crystallized but the addition of small amounts of water

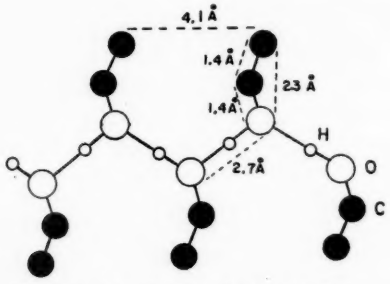


FIG. 1. Structure of absolute alcohol.

renders crystallization extremely difficult. Furthermore, at a given temperature the viscosity is sharply increased by small amounts of water, and the lower the temperature the less water is required for an increase of the same degree. Bernal and Fowler (16) have shown that at low temperatures the oxygen atom of a water molecule can be surrounded by four others, linked to it by hydrogen bonds. It is evident that the oxygen atom of water might equally well be surrounded by four oxygen atoms of ethanol. Therefore, in an alcoholic solution of low water content, we might expect that each water molecule could form the point of linkage of four alcohol chains, if the temperature were low enough. At higher temperatures dissociation would be greater and perhaps only three, or two, alcohol chains would be attached to water. Fig. 2 is a planar diagram

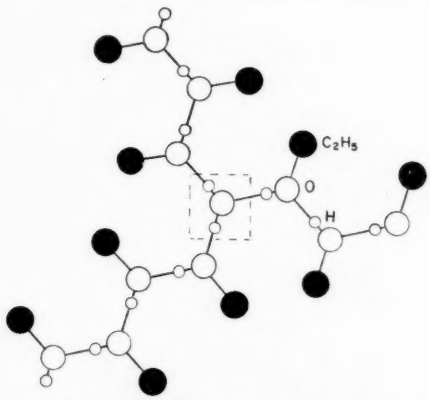


FIG. 2. Structure of "wet" alcohol.

of three ethanol chains linked to a water molecule. Prietzschk has used the viscosity data of Tammann and Hesse (17) to calculate the average length of the alcohol chains linked by water at $-130°$ C.; he finds that there are about 25 molecules of ethanol for each molecule of water, that is, each ethanol chain is six or eight molecules long, depending on whether four or three chains are linked by each water molecule at this temperature.

It is evident that there is a fundamental difference between absolute alcohol and "wet" alcohol, at low temperatures. Pure alcohol is linked only in the form of linear chains but, when water is present, an irregular three-dimensional network is formed which is analogous to the structure in silicate glasses. The lack of the three-dimensional linking in pure ethanol accounts for the comparative ease with which the material is crystallized.

Prietzschk found the powder pattern of solid ethanol to be extremely simple, consisting only of a very broad, intense line, flanked very closely on each side by a sharper but weaker line. Wahl (18) concluded that the crystals of ethanol belong to one of the low symmetry classes but he was unable to obtain further definite information.

As to the ternary system ethanol – water – lithium nitrate, there exists only the isothermal investigation of Campbell and Kartzmark (3) at 25° C., who found no evidence of compound formation between lithium nitrate and ethanol.

EXPERIMENTAL

Purity of Materials

The lithium nitrate was Fisher "Certified Reagent" and it was used without further purification. Water was removed by fusing at least twice. Grinding and transferring were done in a dry-box.

The ethanol used, when absolute alcohol was not required, was purified by distillation through a Podbelniak-type column; the middle third was the only fraction retained. Absolute ethanol was prepared from commercial material by prolonged refluxing with quicklime, followed by treatment of the distillate with magnesium according to the method described by Fieser (19). Absolute alcohol was transferred only in the dry-box. The dryness of the absolute alcohol was constantly tested with aluminum ethoxide by the method of Henle (20), and the density of each new batch was determined.

Methods of Analysis

Lithium nitrate was determined by evaporation to dryness, fusing the residue and weighing. The fusion was repeated at least once, since lithium nitrate is hygroscopic. An accuracy of about 0.1% could be obtained. The ethanol content of a mixture was determined by distilling and determining the density of the distillate.

Apparatus for Thermal Analysis

Glass cells equipped with stirrers and closed from the atmosphere were used. Temperatures were measured with copper–constantan thermocouples, whose e.m.f.'s were recorded by a Brown recording potentiometer. Double or triple copper–constantan junctions were used to increase the sensitivity to the maximum consistent with the range of the recorder. The couples were calibrated from the freezing points of purified, redistilled mercury (f.p. = −38.87° C.), of "spectro" grade carbon tetrachloride (f.p. = −22.8° C.), of reagent grade toluene (f.p. = −95.0° C.), and of "spectro" grade diethyl ether (f.p. = −116.7° C.). Calibration above 0° C. was done by comparison with a previously calibrated mercury-in-glass thermometer reading to 0.1° C.

Both types of freezing-point cell are illustrated in Fig. 3; they differed only in the method of stirring. Both consisted of an inner glass tube containing the solution and surrounded by an outer jacket which could be evacuated as required to reduce the rate of cooling. A well for the thermocouple extended into the solution near the stirrer. The first type of cell (3*a*) was stirred electromagnetically. The second type of cell (3*b*) was used when the viscosity prevented the weaker magnetic stirring of the former type from being effective; most low-temperature work was done in the latter type. Either dry-ice–acetone or liquid nitrogen was used as the cooling agent.

X-Ray Technique

A high-temperature camera of the Buerger type (21) was available and we succeeded in modifying this to take pictures at low temperatures (down to −120° C.). The manner of the modification, and particularly the method of cooling, may be of interest to others; details can be obtained from this laboratory.

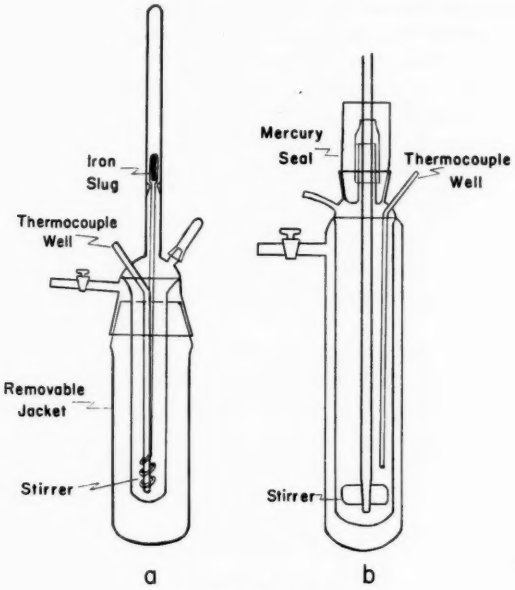


FIG. 3. Freezing-point cells.

EXPERIMENTAL PROCEDURE

The System Lithium Nitrate – Water

This system was submitted to thermal analysis. Since the results showed no indication of the existence of the peritectic point reported by Donnan and Burt (2), and since the work of Campbell and Kartzmark (3) had indicated that the hemihydrate did not exist, X-ray diffraction work was done as an additional check. Diffraction pictures of anhydrous lithium nitrate were taken at room temperature, at 45°, and at 100° C. A second picture was taken at the latter temperature, after prolonged heating, in case any phase transformation occurred slowly. A mixture of lithium nitrate and water was then made up to have a composition corresponding closely to that of the supposed hemihydrate. After this mixture had been maintained at 45° C. for some time, an X-ray diffraction photograph was taken of it.

No diffraction pattern for $LiNO_3.3H_2O$ is listed in the A.S.T.M. index of diffraction patterns, so this compound was photographed at room temperature. For all pictures, copper K_α radiation was used. The standard camera had a diameter of 57.3 mm.

The System Ethanol–Water

In the thermal analysis, little supercooling was encountered in dilute solutions, but as the alcohol content was increased, the supercooling also increased until, beyond 75 weight per cent ethanol, it became extremely difficult to obtain a freezing point at all. Little difficulty from supercooling was encountered with absolute ethanol, but as water was added supercooling increased rapidly.

To investigate the solid phase separating, X-ray diffraction photographs were taken of frozen solutions. Photographs were taken first of ice at temperatures from −20° to −80° C., as a basis of comparison. A series of pictures was also taken of solutions

containing less than 40 weight per cent ethanol, at various temperatures, particularly above the suspected peritectic temperature of −30° C. If any new phase were to appear, it was expected that it would do so beyond 40 weight per cent ethanol and photographs were taken in this region at a series of temperatures and compositions. The composition was not taken beyond 65% ethanol, since the mixture often refused to crystallize beyond this point, nor was the temperature taken below −100° C. All these pictures were taken with copper K_α radiation and an exposure time of about 1.5 hours. Diffraction pictures were also taken of absolute ethanol, both with copper and with iron radiation, at temperatures between −120° and −130° C.

The System Lithium Nitrate – Ethanol

The thermal analysis of this system could not be carried very far because all solutions were very viscous and supercooled extensively; freezing points could only be determined in solutions containing less than about 6% salt. The solubility curve was therefore determined at 50°, 30°, 20°, 0°, and −21° C. The temperature could not be carried lower than this because the extreme viscosity made sampling impossible. During a determination, sampling was made on successive days, but no change in concentration was found. At low temperatures, the mixture was chilled before stirring to prevent possible supersaturation.

The Ternary System Lithium Nitrate – Ethanol – Water

The first approach to the ternary system involved an attempt to follow the eutectic troughs inward from the lithium nitrate – water edge of the diagram but the high viscosity of the solution made sampling impossible. As an alternative a study was undertaken of a number of pseudobinary systems in each of which the ratio of alcohol to water was kept constant and the concentration of lithium nitrate varied. The freezing points of such pseudobinary systems lie on a straight line radiating from the lithium nitrate apex and cutting the ethanol–water edge at the composition of the solution used as solvent. Only the point of first crystallization may be used since, in general, the crystallization path of the solution does not lie along the line of the pseudobinary "cut". Therefore, the pseudobinary eutectic temperatures can be found accurately only if the original solution has the composition of the eutectic. Since it was not considered worth while for the purpose of this investigation to prepare mixtures having the exact pseudobinary eutectic composition, the eutectic halt of a solution near this point was used. When the solid separating is the anhydrous salt, however, the crystallization path does follow the line of the pseudobinary "cut", and true eutectic temperatures can then be obtained. The same applies to peritectic halts, under the same conditions.

Systems having a fixed lithium nitrate – water ratio can be treated in the same way. Accordingly, the freezing points of systems consisting of the hydrate, $LiNO_3.3H_2O$, to which increasing amounts of ethanol were added, were investigated. This system behaves as a true binary system between the compounds $LiNO_3.3H_2O$ and C_2H_5OH, as long as the trihydrate is the stable solid separating.

EXPERIMENTAL RESULTS

The experimental results are contained in Tables I to XIV. The headings are self-explanatory.

DISCUSSION OF RESULTS

The System Lithium Nitrate – Water

The results, as listed in Table I and shown graphically in Fig. 4, are not in complete

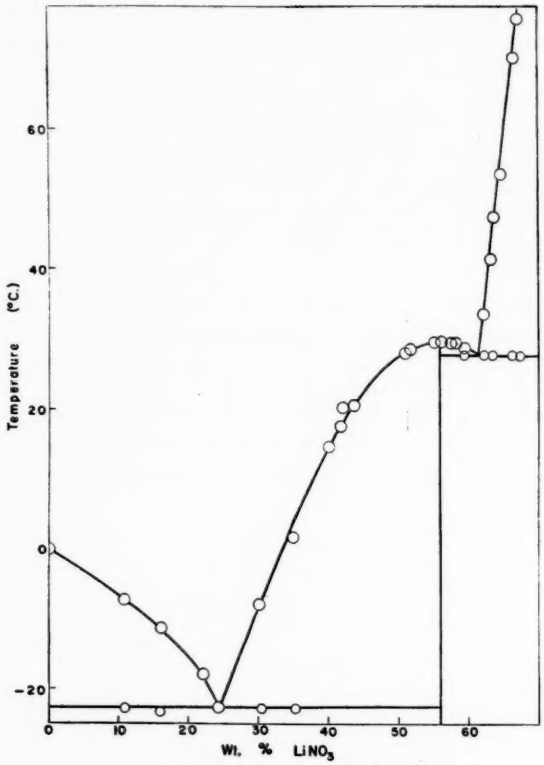


FIG. 4. The system $LiNO_3$–H_2O.

TABLE I

THERMAL ANALYSIS DATA OF THE SYSTEM LITHIUM NITRATE – WATER

Wt. % $LiNO_3$	Freezing point, ° C.	Invariant point, ° C.	Solid phases present at freezing point
10.7	−7.4	−22.8	Ice
16.0	−11.3	−23.4	"
22.3	−17.7		"
24.5		−22.9	Ice + $LiNO_3.3H_2O$
30.1	−7.9	−22.9	$LiNO_3.3H_2O$
35.1	1.5	−22.9	"
40.1	14.5		"
41.8	17.5		"
42.1	20.2		"
43.7	20.6		"
51.3	28.4		"
55.2	29.4		"
56.0	29.6		"
57.8	29.5		"
58.0	29.5		"
59.6	28.8	27.9	"
62.3	33.6	27.9	$LiNO_3$
63.4	41.3	27.9	"
63.6	47.1	27.9	"
64.6	53.7	27.9	"
66.4	70.0	27.9	"
66.9	75.6	27.9	"

agreement with those of Donnan and Burt (2). The ice–trihydrate eutectic lies at −22.9° C. and 24.5 weight per cent lithium nitrate; this is at both a lower temperature and a lower concentration than reported by Donnan and Burt (−17.8° C., 33 weight per cent lithium nitrate). The values for the higher eutectic, 27.9° C. and 61.5 weight per cent lithium nitrate, are also different from those previously accepted (29.6° C., 59 weight per cent $LiNO_3$). Here, trihydrate is in equilibrium with anhydrous lithium nitrate (and solution) and not with hemihydrate, as the previous study had supposed. The melting point of lithium nitrate trihydrate was found to be 29.6° C.

All the X-ray pictures taken on anhydrous lithium nitrate between room temperature and 100° C. were identical, showing that only one phase of anhydrous salt exists between these temperature limits. A mixture of lithium nitrate and water, corresponding in composition to the supposed hemihydrate, gave only the pattern of anhydrous salt (above 27.9° C.). This evidence, together with the observations of Campbell and Kartzmark (3), refutes the claim that a hemihydrate exists.

The X-ray powder diffraction pattern for $LiNO_3.3H_2O$ is listed in Table II. Relative intensities were estimated visually, the strongest line being assigned an intensity of 10. The trihydrate pattern has many lines in common with the anhydrous salt.

TABLE II

X-RAY POWDER DIFFRACTION PATTERN OF $LiNO_3.3H_2O$

Relative intensity	Lattice spacing, Å
2	6.13
7	4.20
3	3.47
10	2.99
2	2.79
2	2.68
1	2.53
5	2.37
8	2.13
1	2.02
1	1.90
2	1.80
3	1.71
2	1.54
	1.36

The System Ethanol–Water

The results of thermal analysis are listed in Table III and the equilibrium diagram is shown in Fig. 5. It was found that supercooling increased with ethanol content and became extremely persistent beyond 75 weight per cent ethanol, where it was impossible to detect an initial freezing point although eutectic halts could be obtained with solutions up to the eutectic composition. On the alcohol side of the eutectic, supercooling and viscosity increased with increasing water content but reasonably good freezing points could be observed up to the eutectic point. No eutectic halts were obtained in this region and this may be an indication that the solid solution formation reported by Pushin (10) does indeed exist.

Formation of solid solution is most common between substances having similar crystal structure, although this is by no means a necessary condition. Ice crystallizes in the hexagonal system but, although the structure of the ethanol molecule is known, nothing is known about the crystal structure of solid alcohol; the direct observations of Wahl

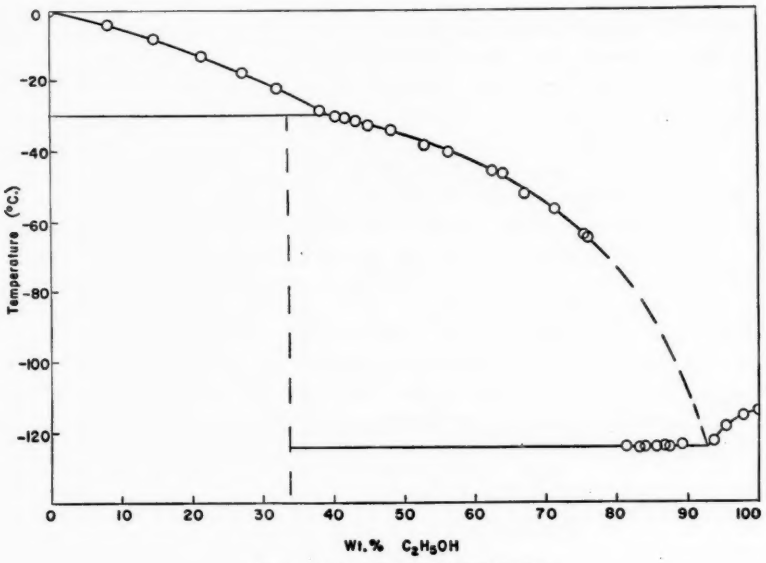


FIG. 5. The system ethanol–water.

TABLE III

THERMAL ANALYSIS DATA OF THE SYSTEM C_2H_5OH–H_2O

Composition, wt. % C_2H_5OH	Freezing point, °C.	Invariant point, °C.
8.1	−3.8	
14.8	−7.4	
21.4	−12.7	
27.1	−17.9	
32.1	−22.4	
38.1	−28.3	
40.4	−30.3	
41.6	−30.8	
43.2	−31.8	
45.1	−33.1	
48.3	−34.2	
53.0	−38.6	
56.3	−40.8	
62.5	−45.7	
64.0	−46.5	
67.1	−52.6	
71.3	−56.1	
75.5	−64.0	
75.8	−64.6	
81.1	—	−124.1
82.7	—	−124.4
83.9	—	−124.1
85.6	—	−124.1
86.8	—	−124.1
87.4	—	−124.6
88.1	—	−123.8
93.6	−122.9	
95.4	−118.6	
97.8	−115.7	
100.0	−114.4	

(18) indicate that solid ethanol has a very unsymmetrical form. This may easily be so, if the crystal is made up from the irregular chains of ethanol molecules which Prietzschk (14) has shown to be present in the cold liquid. It would then be possible for water to enter such a crystal lattice as part of an alcohol chain, or even as the point of linkage of two or more chains, since Prietzschk shows that such linkage certainly occurs in the "wet" liquid. Formation of solid solutions of ice in ethanol may thus be accounted for without the assumption of similar crystal structures.

The freezing-point curve shows the inflection previously found by Tarassenkov (11) and by Shalberov *et al.* (12) but no peritectic halt was ever observed. The inflection occurs at −30° C. and 39.5 weight per cent ethanol. We find the eutectic to lie at −124.1° C. and about 93.0 weight per cent ethanol, whereas Pushin and Glagoleva (10) reported the values −118° C. and 93.5 weight per cent ethanol, for this point. The freezing point of absolute ethanol was found to be −114.4° C., agreeing within the experimental error with the generally accepted value of −114.6° C.

The results of X-ray diffraction studies at low temperatures are collected in Tables IV, V, and VI, which list the spacings and intensities of the lines from diffraction photographs of ice, of dilute ethanol solutions (i.e. solutions containing less than 30% by weight of ethanol), and of more concentrated ethanol solutions, respectively. The pictures in all cases showed much background darkening and the lines were quite broad, since it

TABLE IV

X-RAY POWDER DIFFRACTION PATTERN OF ICE

Observed values (mean of 4 pictures)		Literature values	
Lattice spacing *d*, Å	Relative intensity	Lattice spacing *d*, Å	Relative intensity
4.14	Very weak	3.92	10
3.92	Medium	3.67	100
3.55	Strong	3.44	20
2.70	Medium	2.67	15
2.30	Medium	2.26	10
2.11	Strong	2.07	50
1.95	Strong	1.92	10
1.45	Very weak	1.52	15
1.39	Weak	1.37	2
1.27	Very weak	1.30	3
		1.25	3
		1.17	5

TABLE V

X-RAY POWDER DIFFRACTION PATTERN OF FROZEN SOLUTIONS CONTAINING LESS THAN 40 WT. % ETHANOL AT TEMPERATURES ABOVE −30° C.
(mean of 8 pictures)

Lattice spacing *d*, Å	Relative intensity	Number of times observed
4.18	Very weak	3
3.92	Weak	4
3.76	Very weak	3
3.54	Strong, diffuse	8
2.69	Medium	8
2.30	Strong	5
2.13	Medium	6
1.39	Weak	5

TABLE VI

X-RAY POWDER DIFFRACTION PATTERN OF FROZEN SOLUTIONS CONTAINING MORE THAN 40 WT. % ETHANOL AT TEMPERATURES FROM −30° C. TO −90° C.
(mean of 10 pictures)

Lattice spacing d, Å	Relative intensity	Number of times appearing
3.61	Weak, diffuse	6
3.32	Strong	10
2.97	Strong	8
2.64	Very weak	2

was necessary to use wide capillaries to prevent separation of the liquid column on cooling, so that no great accuracy in the measurements of the spacings could be obtained. Although the nominal diameter of the camera was 57.3 mm., the fact that the ice pattern, the mean of four pictures, has spacings consistently larger than those listed in the A.S.T.M. index and determined by Dennison (22) and by Barnes (23) indicates either that the camera is slightly smaller than the figure given above or that shrinkage of the film occurred. No attempt was made to calibrate the camera, since only comparative results were desired and, in any case, the discrepancy is not large. Neither the strong line of spacing $d = 3.67$ Å nor the weaker line at $d = 3.44$ Å could be found but a strong line was observed at $d = 3.55$ Å and this is probably equivalent to the two missing lines. A very weak line at $d = 4.14$ Å, which does not appear in the literature tabulation, also occurred.

The diffraction patterns of dilute alcohol solutions taken under such conditions that no compound could be formed (i.e., at temperatures above that of the point of inflection) were not good. The lines were quite diffuse, largely owing to unfrozen liquid in the tests. The results agree fairly well with the literature tabulation for ice, although an additional line at $d = 3.76$ Å appeared in three cases and many of the weaker lines were absent.

The pattern given by solutions containing more than 40% by weight ethanol is listed in Table VI. A total of 10 pictures containing distinguishable lines were used. These pictures were little better than those taken in dilute solutions and the lines were particularly broad, since in general wider capillaries were required for such solutions. Few lines were obtained; only three appeared at all consistently. Of these, the first, at $d = 3.61$ Å, lies close to the position of a strong line in the ice pattern. Since this line is both weak and diffuse, there is the possibility that it is due to ice deposited on the outside of the capillary, from moisture present in the camera at the beginning of the run, but it is difficult to see how enough ice could be deposited in this way to give an observable line; it is probably a true line from the specimen. The other two lines, both strong and both nearly always present, are quite far removed from any ice lines. This is particularly true of that falling at $d = 2.97$ Å. The other line falls at $d = 3.32$ Å. These two lines were predominant on the diffraction patterns of solutions of alcohol exceeding 40 weight per cent ethanol and taken at temperatures between −35° C. and −90° C. The temperature was never taken as low as the freezing point of ethanol, so the lines cannot be due to solid alcohol. Moreover, they do not appear on any picture of ice at any temperature, or of more dilute solutions of alcohol at temperatures above −30° C. They can only be explained by the formation of a new solid phase separating from solution. They indicate that an incongruently melting hydrate of ethanol may be formed and that therefore the point of inflection on the freezing curve is a true peritectic point.

A few solutions of roughly the expected composition of the hydrate, $C_2H_5OH.5H_2O$, were made up and photographed at temperatures well below the supposed peritectic temperature. These pictures showed only the ice pattern, whereas, if a compound is formed, lines from it also should be present. This behavior can only be explained if the system cools metastably past the peritectic temperature, the reaction "ice + solution → compound" failing to take place. The absence of a peritectic halt on the cooling curve can be explained in the same way. The spacings measured from these diffraction patterns are not highly accurate and any picture alone would be of doubtful value because of the broad lines and the generally dark background. As a group, however, the results are consistent, and errors in the spacings listed are not great enough to invalidate the general conclusion.

The question of the composition of this hypothetical hydrate of ethanol cannot be answered with certainty. The position of the point of inflection corresponds to an alcohol: water ratio of 3.98, but the compound must contain more water than this. Although the formula $C_2H_5OH.4H_2O$ is possible, it is unlikely, since this composition is so close to the composition of the peritectic point. Perhaps the most probable formula is that proposed by Shalberov (12), viz. $C_2H_5OH.5H_2O$.

The diffraction photographs of absolute ethanol resulted only in a single broad line of strong intensity at $d = 3.89$ Å. This is the result of two pictures, one taken with copper, the other with iron, radiation. The latter was used in the hope that it would result in the resolution of the single line into the closely spaced triplet observed by Prietzschk (14), but it did not. The position of the single line was similar to that of the triplet in the photograph published by Prietzschk but, unfortunately, he does not indicate any spacings.

The System Lithium Nitrate – Ethanol

The results obtained by thermal analysis are shown in Table VII. Only quite dilute solutions could be frozen, the supercooling increasing with lithium nitrate content. No eutectic halt could be detected. Solubility measurements are summarized in Table VIII.

TABLE VII

THERMAL ANALYSIS DATA OF THE SYSTEM $LiNO_3$–C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.
0.0	−114.4
0.8	−115.8
2.1	−116.7
3.8	−118.2
5.5	−118.6
6.3	−124

TABLE VIII

SOLUBILITY DATA OF THE SYSTEM $LiNO_3$–C_2H_5OH

Temperature, ° C.	Solubility, wt. % $LiNO_3$
50.0	25.6
30.1	24.7
20.1	24.0
0.0	23.0
−21	21.9

A plot of freezing point and solubility data, as in Fig. 6, shows that, in order that the two curves may intersect without compound formation, the eutectic point must lie unusually far into the diagram. For systems involving substances whose melting points are so dissimilar as are those of ethanol and lithium nitrate, it is seldom that the eutectic lies more than a short distance from the axis of the lower-melting compound. It is therefore quite possible that an alcoholate of lithium nitrate may exist in the solid state.

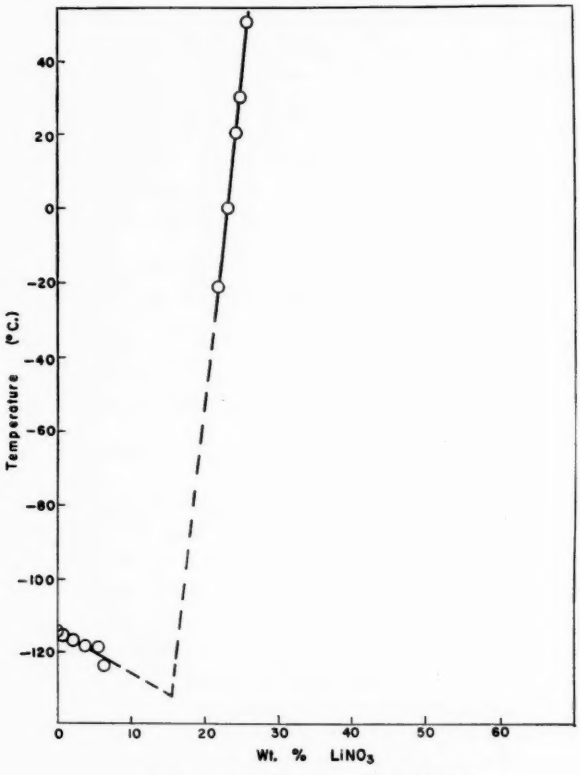


FIG. 6. The system $LiNO_3$–C_2H_5OH.

The very great viscosity of alcoholic lithium nitrate solutions at low temperatures indicates some sort of interaction between ethanol and lithium nitrate. It is very probable that the strongly electropositive lithium ion and the electronegative oxygen of the alcohol will exhibit strong electrostatic attraction, just as do lithium ion and water. Since at low temperatures the ethanol molecules are linked in chains, the lithium ions could be solvated by a number of these chains and they would, in effect, form the points of linkage of them.

The System Lithium Nitrate – Ethanol – Water

Five pseudobinary "cuts" in which lithium nitrate was dissolved in solvents of fixed ethanol: water ratio were made through the ternary system. The solvents were 27.2,

42.0, 49.7, 66.4, and 78.2 weight per cent ethanol. Tables IX to XIII give the thermal analysis data, while Figs. 7 to 11 show the freezing-point curves which were obtained. It was found that supercooling increased with alcohol content except when anhydrous lithium nitrate was the solid phase, when it was nearly negligible even in solutions containing considerable quantities of alcohol. Supercooling was especially pronounced with solutions in 78.2% ethanol, and freezing points below −20° C. could not be obtained.

The system lithium nitrate trihydrate - ethanol is shown in Fig. 12 and the thermal analysis data are given in Table XIV. Some of the points are taken from the freezing-point curves of the other pseudobinary systems.

Figs. 13 and 14 show the ternary system as a whole, so far as we have been able to determine it. In Fig. 13, a series of isothermal solubility lines are depicted. These were obtained from the various pseudobinary "cuts" by reading off the compositions corresponding to each temperature. Isothermals at 25°, 20°, 15°, 10°, 0°, −15°, −35°, and

TABLE IX

THERMAL ANALYSIS DATA OF THE PSEUDOBINARY SYSTEM
$LiNO_3$ - 27.2 WT. % C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.	Pseudoinvariant point, ° C.
0.0	−17.8	
8.5	−25.0	
10.2	−27.1	
12.7	−30.1	
15.0	−35.3	
17.6	−26.9	−41.1
20.3	−16.6	
24.3	−4.6	
35.4	13.0	
48.6	25.0	
52.2	25.3	
57.9	50.6	22.1
56.7	38.7	22.3

TABLE X

THERMAL ANALYSIS DATA OF THE PSEUDOBINARY SYSTEM
$LiNO_3$ - 42.0 WT. % C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.	Pseudoinvariant point, ° C.
0.0	−30.6	
5.6	−38.8	
9.7	−44.9	
12.5	−41.8	−51.0
14.1	−34.7	
33.8	15.5	
39.6	21.3	
40.3	(~21)	
42.8	22.4	
47.0	22.1	
48.7	21.6	
51.0	21.3	
52.3	35.6	20.7
54.0	46.2	21.0

−60° C. are shown, as well as the line in the ice region at −20° C. In Fig. 14, only the eutectic and peritectic troughs are shown. Again, the composition data were obtained from the pseudobinary cuts.

Some uncertain indications, not described here, have been obtained of the existence of a ternary compound (incongruently melting), such as $LiNO_3.2C_2H_5OH.H_2O$, but the evidence is extremely inconclusive.

It is reasonably certain that no alcoholate of lithium nitrate crystallizes from solutions of less than 50 weight per cent ethanol, but in more concentrated alcohol solutions the nature of the solid phase is uncertain. When the solvent contained more than 80% ethanol, pronounced supercooling made experimental study impossible.

TABLE XI

THERMAL ANALYSIS DATA OF THE PSEUDOBINARY SYSTEM $LiNO_3$ – 49.7 WT. % C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.	Pseudoinvariant point, ° C.
0.0	−36.0	
3.0	−43.4	
8.0	−48.7	
10.4	−54.2	−58.9
14.1	−33.7	
19.7	−12.4	
36.0	18.8	
37.0	19.2	
38.5	20.1	
43.7	21.8	
45.7	21.3	
48.5	23.6	19.8
48.8	30.1	19.5

TABLE XII

THERMAL ANALYSIS DATA OF THE PSEUDOBINARY SYSTEM $LiNO_3$ – 66.4 WT. % C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.	Pseudoinvariant, point, ° C.
0.0	−47.4	
4.9	−57.9	
6.8	−63.2	
9.0		−73.0
10.2	−62.0	
13.8	−27.0	
15.5	−18.2	
18.3	−7.8	
23.2	4.4	
26.6	10.3	
27.0	11.0	
29.6	13.8	
29.7	14.1	12.1
30.9	15.6	12.5
35.6	17.5	
35.7	17.3	
40.0	16.6	
43.0	31.1	15.0
43.9	43.1	14.6

TABLE XIII

THERMAL ANALYSIS DATA OF THE PSEUDOBINARY SYSTEM
$LiNO_3$ - 78.2 WT. % C_2H_5OH

Composition, wt. % $LiNO_3$	Freezing point, ° C.	Pseudoinvariant point, ° C.
16.6	−13.2	
17.9	−6.3	
21.5	−1.3	
24.4	0.8	
26.2	1.6	
27.4	2.5	
30.6	5.4	
31.4	5.6	
32.6	(~5.2)	
32.8	11.3	
34.5	24.0	(~5)
35.1	28.8	5.7
35.2	31.9	
36.2	43.5	5.1

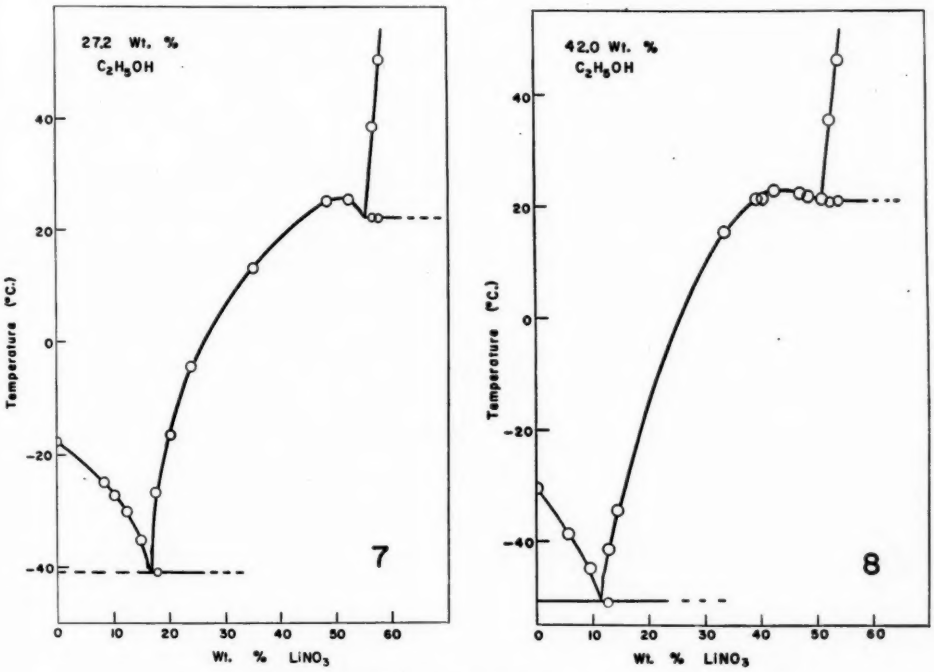
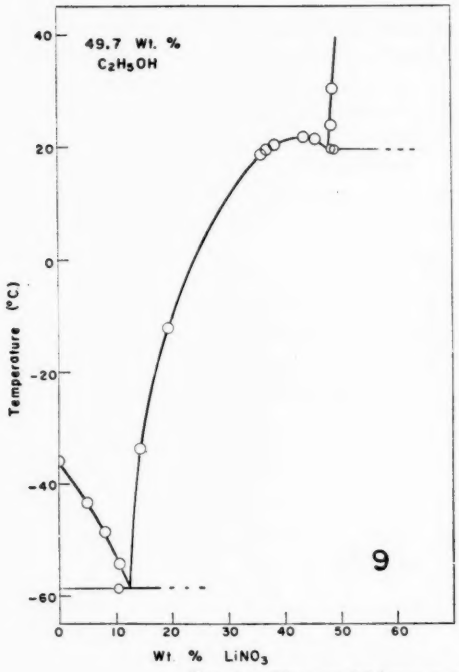


FIG. 7. The pseudobinary system.
FIG. 8. The pseudobinary system $LiNO_3$ - 42.0 wt. % C_2H_5OH.



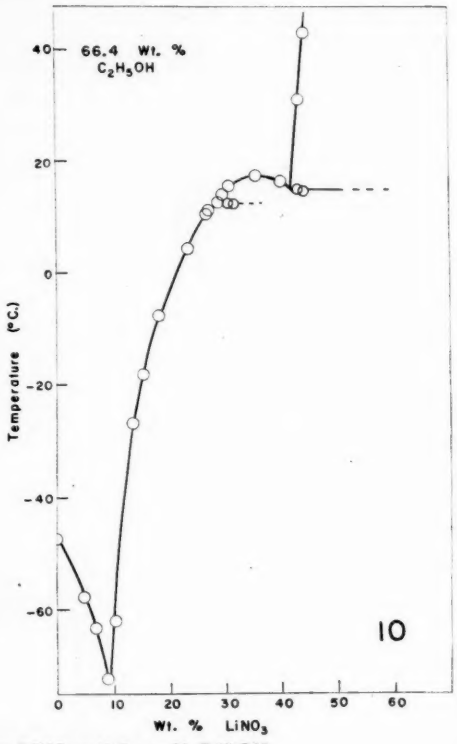
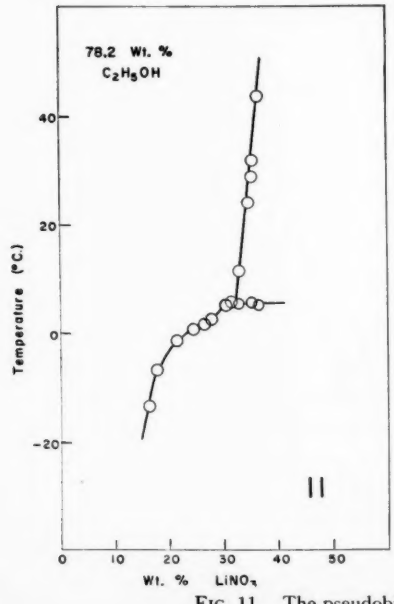


FIG. 9. The pseudobinary system $LiNO_3$ – 49.7 wt. % C_2H_5OH.
FIG. 10. The pseudobinary system $LiNO_3$ – 66.4 wt. % C_2H_5OH.



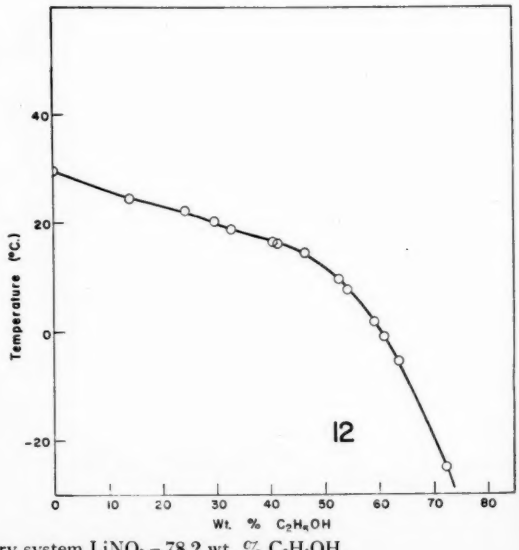
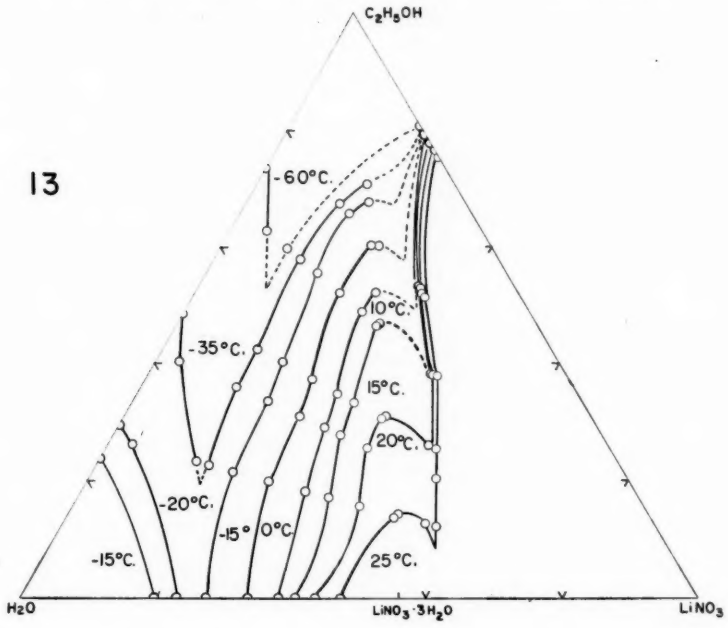


FIG. 11. The pseudobinary system $LiNO_3$ – 78.2 wt. % C_2H_5OH.
FIG. 12. The system $LiNO_3.3H_2O$–C_2H_5OH.



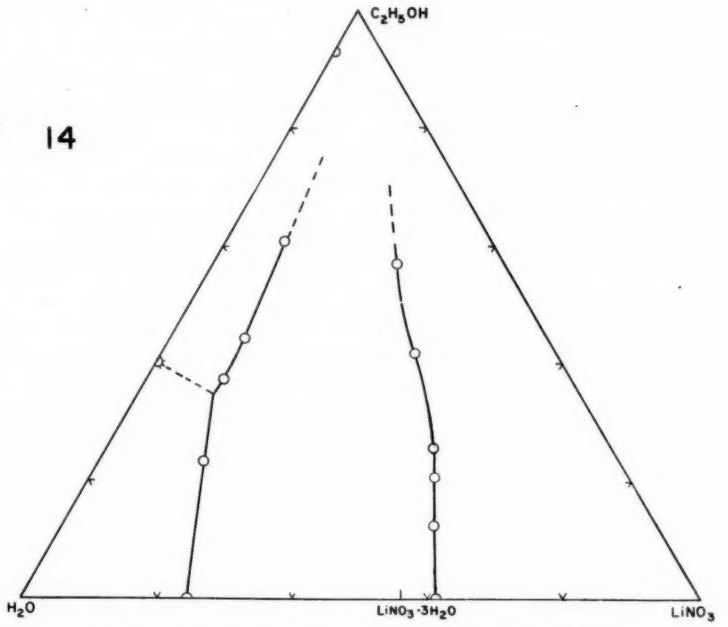


FIG. 13. Solubility isotherms in the system $LiNO_3$–C_2H_5OH–H_2O.
FIG. 14. Eutectic troughs in the system $LiNO_3$–C_2H_5OH–H_2O.

TABLE XIV

THERMAL ANALYSIS DATA OF THE SYSTEM $LiNO_3.3H_2O$–C_2H_5OH

Composition, wt. % C_2H_5OH	Freezing point, ° C.
0.0	29.6
14.2*	24.2
24.4*	22.4
30.0*	20.2
32.9	18.8
40.9	16.3
41.1	16.1
46.8*	14.5
52.6	9.7
54.4	7.7
59.0	1.7
61.8*	−1.0
67.3	−5.2
72.2	−25.0

**Values interpolated from pseudobinary cuts.*

ACKNOWLEDGMENTS

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THE CONDENSATION OF FURAN WITH CARBONYL COMPOUNDS[1]

WILLIAM H. BROWN AND WARREN N. FRENCH[2]

ABSTRACT

A homologous series of substituted quaterenes has been synthesized by the condensation of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] with keto acids and their esters. Substituted quaterenes containing chlorine have also been prepared. Only one out of the theoretically possible four geometrical isomeric quaterenes which could arise from the condensation of furan with butanone has been isolated. In all instances where more than one geometrical isomeric quaterene would be theoretically possible, only one has been isolated. Two new dinitro compounds have been prepared by the nitration of 2,2-difurylbutane and 3,3-difurylpentane.

Recently, Ackman, Brown, and Wright (1) reported the formation of difurylalkanes by the condensation of furan with the corresponding methyl ketone in the presence of hydrochloric acid. Brown and Sawatzky (2) and Beals and Brown (3) have extended the series to include the condensation of furan with aldehydes, chlorinated aldehydes and ketones, keto acids, and 3-pentanone.

The difurylalkane, 2,2-difurylpropane, has been isolated from the reaction mixture of furan with acetone. Subsequent reaction between two molecules of 2,2-difurylpropane and two molecules of acetone with the elimination of two molecules of water leads to the formation of a cyclic compound (II; R, R_1, R_2, R_3 = Me) composed of four residues each of furan and acetone. This cyclic compound has been assigned the trivial name "octamethyl-tetroxaquaterene". "Quaterene" denotes a closed system composed of four methylene-bridged 1,4-disubstituted cyclopentadienes (1). Another product of the condensation of furan with acetone is 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] (I; R, R_1, R_2 = Me), which condenses with one molecule of acetone to form the same octamethyl-tetroxaquaterene.

In the present investigation, two quaterenes containing chlorine were synthesized. Treatment of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] [I; R, R_1, R_2 = Me) with chloroacetone in the presence of hydrochloric acid gives the expected 2-chloromethyl-2,7,7,12,12,17,17-heptamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1, R_2 = Me; R_3 = CH_2Cl). The other quaterene containing chlorine, 2,12-*bis*(chloromethyl)-2,7,7,12,17,17-hexamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1 = Me; R_2, R_3 = CH_2Cl), is formed by the condensation of 2,2-difurylpropane with chloroacetone. While two geometric isomers (*cis* and *trans*) of the latter quaterene are possible, only one was found. A compound having the same structure would also be expected as a result of the condensation of 2,2-difuryl-1-chloropropane with acetone. This possibility has been previously investigated (4). No reaction was observed.

The presence of halogen in the carbonyl compound appears to inhibit the above condensations since lower yields of the condensation product are obtained when chloroacetone is used in place of acetone. Chlorinated aldehydes and ketones containing two or more chlorine atoms, such as *sym*dichloroacetone, do not undergo complete condensation with I (R, R_1, R_2 = Me) to form quaterenes. The reaction probably proceeds to the carbinol stage but further condensation is prevented by the negative chlorine atoms. Carbinol formation has been demonstrated by Willard and Hamilton (5). They found that furan condenses with chloral to form 1-furyl-2,2,2-trichloroethanol.

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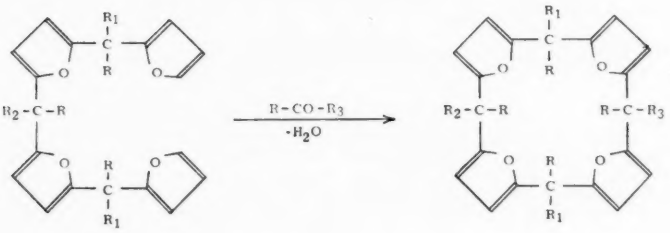
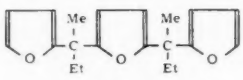
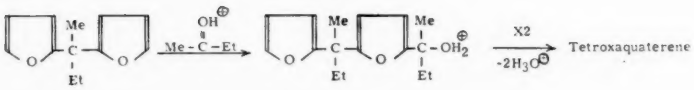


I II



III



IV V

Other substituted quaterenes are formed by the condensation of keto acids or their esters with 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] (I; R, R_1, R_2 = Me). Thus pyruvic acid, methyl and ethyl acetoacetate, levulinic acid, and methyl levulinate react with I (R, R_1, R_2 = Me) to give the corresponding substituted tetroxaquaterenes. Since the condensations were all carried out using absolute alcohols as the reaction solvent and hydrogen chloride as the condensing agent, esterified products resulted: viz., methyl and ethyl esters. Transesterification can also occur during the reaction since the condensation of I (R, R_1, R_2 = Me) with methyl levulinate results in the formation of the corresponding ethyl ester with ethanol as the reaction solvent. The products are listed in Table I. Each

TABLE I

CONDENSATION PRODUCTS FROM 2,2-ISOPROPYLIDENE*bis*[5-(DIMETHYLFURFURYL)FURAN] AND KETO ACIDS

Substituent at the No. 2 position on the tetroxaquaterene	% yield	Melting point	Molecular formula	Analysis	
				Calc.	Found
				Methoxyl	
Carbomethoxy	15	172.5	$C_{29}H_{32}O_6$	6.51	6.42
Carbomethoxymethyl	17	179.0	$C_{30}H_{34}O_6$	6.32	6.15
Carbomethoxyethyl	34	157.5	$C_{31}H_{36}O_6$	6.15	6.13
				Ethoxyl	
Carbethoxy	39	169.5	$C_{30}H_{34}O_6$	9.19	9.22
Carbethoxymethyl*	49	165.0	$C_{31}H_{36}O_6$	8.93	8.81
Carbethoxyethyl	63	153.0	$C_{32}H_{38}O_6$	8.69	8.87
Carboxy		Decomp. 250	$C_{28}H_{30}O_6$		
Carboxymethyl		248.5–249.5	$C_{29}H_{32}O_5$		
Carboxyethyl		225.5–226.5	$C_{30}H_{34}O_6$		

**Anal. Calc. for* C, 73.8; H, 7.19; *mol. wt., 505. Found:* C, 73.8; H, 7.18; *mol. wt., 522.*

ethyl ester condensation product was hydrolyzed to the corresponding free acid and then treated with diazomethane to give the methyl ester. The same methyl ester is formed by the condensation of I (R, R_1, R_2 = Me) with a keto acid or methyl ester in methanol.

Inspection of Table I shows that the carboxyl group exerts a deactivating influence on the condensation when in proximity to the carbonyl group. Thus pyruvic acid gives a lower yield than levulinic acid under similar conditions. Yields are also lower when methanol rather than ethanol is the reaction solvent, probably owing to greater furan ring fission by methanolic hydrogen chloride than by ethanolic hydrogen chloride.

Ackman, Brown, and Wright (1) have also investigated the condensations of furan with butanone, methyl *n*-propyl ketone, methyl isobutyl ketone, and methyl *n*-amyl ketone. In each case, only one out of the possible four geometric isomers of the tetroxaquaterene has been isolated. One would expect to find more than one geometric isomer since the condensation of 2,2-difurylbutane with acetone yields the two expected geometric isomers (*cis* and *trans*) in the ratio of about 8 to 1 (1). A search for other isomers was considered to be important because of the alternative paths of formation of a tetroxaquaterene by the condensation of either I or a difurylalkane with the parent ketone.

In the present investigation, a search for additional isomeric tetroxaquaterenes was made in the reaction mixture resulting from the condensation of furan with butanone. The progenitor of the reaction, 2,2-difurylbutane, has previously been isolated (1). It condenses with butanone to form only one geometric isomer of 2,7,12,17-tetraethyl-2,7,12,17-tetramethyl-21,22,23,24-tetroxaquaterene (II; R = Me; R_1, R_2, R_3 = Et). A third product, thought to be 2,5-*bis*(ethylmethylfurfuryl)furan (III), has now been isolated from the condensation of furan with butanone. It is not a direct intermediate in the formation of the tetroxaquaterene. A fourth compound which was obtained by us is 2,2-butylidene-*bis*[5-(ethylmethylfurfuryl)furan] (I; R = Me; R_1, R_2 = Et) which condenses with butanone to yield a single tetroxaquaterene identical with the one formed from 2,2-difurylbutane and butanone. No additional isomeric tetroxaquaterenes were found in the original reaction mixture.

An inspection of the formula of I (R = Me; R_1, R_2 = Et) shows that it could exist as three diastereomers, one of which should be resolvable. Similarly, III could exist as two diastereomers, one of which should be resolvable. However, only one form of each was isolated by fractional distillation of the reaction products. Attempts to form derivatives of I (R = Me; R_1, R_2 = Et) and III having a functional group suitable for resolution purposes were unsuccessful. Nitration, aminomethylation, and acetylation reactions all gave resinous products while the condensation of I (R = Me; R_1, R_2 = Et) with keto acids gave products in insufficient yield for resolution.

The absence of possible geometric isomers of substituted quaterenes has also been noted in the pyrrole series. Chelintzev and Tronov (6) have reported that only two of the four theoretically possible isomers are obtained from the condensation of pyrrole with butanone. One geometric isomer was found to be in preponderance.

The existence of only one isomeric form of the quaterene from furan and butanone implies that the condensation is strongly influenced by steric factors which compel the reaction to proceed in such a manner as to form only one geometric isomer.

Two new dinitro compounds, 2,2-*bis*(5-nitrofuryl)butane and 3,3-*bis*(5-nitrofuryl)-pentane, have been prepared from the corresponding difurylalkanes using a nitration procedure typical for furans. The other member of the series, 2,2-*bis*(5-nitrofuryl)propane, has been previously reported (1). The data for these compounds are recorded in Table II.

Although the nitration of 1,1-difurylethane appears to proceed normally, the products are quite unstable.

TABLE II

NITRATION PRODUCTS OF DIFURYLALKANES

Compound nitrated	% yield	Melting point	Molecular formula	Analysis, % N	
				Calc.	Found
1,1-Difurylethane		No product isolated			
2,2-Difurylpropane (1)	57	135.0–135.5	$C_{11}H_{10}N_2O_6$	10.53	10.33
2,2-Difurylbutane	59	84.0–84.5	$C_{12}H_{12}N_2O_6$	10.00	9.40
3,3-Difurylpentane	67	120.0–120.5	$C_{13}H_{14}N_2O_6$	9.52	9.10

EXPERIMENTAL

All melting points have been corrected against reliable standards. Molecular weights were determined by the Rast method. A typical preparative method for the substituted quaterenes listed in Table I is given for the condensation of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] (I; R, R_1, R_2 = Me) with levulinic acid and its methyl ester. The other substituted quaterenes in Table I may be obtained by a similar procedure using acetoacetic esters or pyruvic acid. The nitrated difurylalkanes were prepared by the method of Ackman, Brown, and Wright (1).

2-Chloromethyl-2,7,7,12,12,17,17-heptamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1, R_2 = Me; R_3 = CH_2Cl)

A solution of 0.4 g. (0.001 mole) of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] (I; R, R_1, R_2 = Me) and 0.93 g. (0.01 mole) of chloroacetone in 5 ml. of commercial absolute ethanol was saturated with anhydrous hydrogen chloride gas. The solution turned deep red and crystals began to form immediately. The solid was filtered off and washed with 5 ml. of ethanol to give 0.26 g. (56%) of crude product, m.p. 214°–216°. Crystallization from an ethanol–benzene mixture gave 0.20 g. (43%) of white needles, m.p. 219.5°–220.0°. Anal. Calc. for $C_{28}H_{31}ClO_4$: Cl, 7.60; mol. wt., 467. Found: Cl, 7.80; mol. wt., 475.

2,12-Bis(chloromethyl)-2,7,7,12,17,17-hexamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1 = Me; R_2, R_3 = CH_2Cl)

A solution of 1.76 g. (0.01 mole) of 2,2-difurylpropane and 0.93 g. (0.01 mole) of chloroacetone in 10 ml. of absolute ethanol was saturated with anhydrous hydrogen chloride gas. The solution turned a deep red and solid material began forming in 2 hours. After 2 days, a sticky yellow material was filtered off and successively leached with 10-ml. portions of boiling ethanol. The first leaching contained 0.26 g. of sticky yellow material, and the following seven a total of 0.29 g. (11.5%) of white needles. Crystals from the second extract had a m.p. of 201.0°–203.5°, while those from the seventh had a m.p. of 211.0°–211.5°. The crystalline products were combined and crystallized from a 1:1 ethanol:benzene mixture (20 ml./g.) to give 0.15 g. (6.0%) of white needles, m.p. 211.0°–211.5°. Anal. Calc. for $C_{28}H_{30}Cl_2O_4$: Cl, 14.1; mol. wt., 501. Found: Cl, 14.0; mol. wt., 498.

2-Carbethoxyethyl-2,7,7,12,12,17,17-heptamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1, R_2 = Me; R_3 = $CH_2CH_2COOC_2H_5$)

A solution of 1.0 g. (0.00025 mole) of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] (I; R, R_1, R_2 = Me) and 0.58 g. (0.005 mole) of levulinic acid in 10 ml. of absolute ethanol was saturated with anhydrous hydrogen chloride gas. The solution became deep red and

cloudy within 3 minutes. After 20 hours, the mixture was filtered to give 0.93 g. of a yellow solid. Crystallization from ethanol gave 0.77 g. (63%) of light yellow crystals, m.p. 146.0°–147.5°. A second crystallization, including treatment with charcoal, resulted in 0.49 g. (40%) of white needles, m.p. 153°. Anal. Calc. for $C_{32}H_{38}O_6$: OC_2H_5, 8.69; mol. wt., 519. Found; OC_2H_5, 8.87; mol. wt., 517.

2-Carboxyethyl-2,7,7,12,12,17,17-heptamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1, R_2 = Me; R_3 = CH_2CH_2COOH)

A solution of 0.25 g. (0.00048 mole) of the ethyl ester obtained as above in 20 ml. of *N*/1 solution of ethanolic potassium hydroxide was refluxed for 2 hours. After acidifying with glacial acetic acid, water was added until the saturation point was reached. On cooling, the resulting solid was removed by filtration and crystallized from benzene to give 0.11 g. (45%) of white needles, m.p. 225.5°–226.0°.

2-Carbomethoxyethyl-2,7,7,12,12,17,17-heptamethyl-21,22,23,24-tetroxaquaterene (II; R, R_1, R_2 = Me; R_3 = $CH_2CH_2COOCH_3$)

(*a*) *From 2,2-isopropylidenebis[5-(dimethylfurfuryl)furan] and levulinic acid in methanol.*—A solution of 0.4 g. (0.001 mole) of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] and 0.58 g. (0.005 mole) of levulinic acid in 5 ml. of absolute methanol was saturated with hydrogen chloride gas. The solution slowly turned deep red with the formation of a yellow oil. Solid material began forming after 30 minutes. After 22 hours, a light yellow solid was removed by filtration. Crystallization from methanol, including treatment with charcoal, gave 0.17 g. (34%) of white needles, m.p. 157.5°. Anal. Calc. for $C_{31}H_{36}O_6$: OCH_3, 6.15. Found: OCH_3, 6.13.

(*b*) *From treatment of the acid* (II; R, R_1, R_2 = Me; R_3 = CH_2CH_2COOH) *with diazomethane.*—A solution of 0.10 g. of the acid obtained as above in ether was treated with an ethereal solution of diazomethane to give a product with a melting point of 157.5°. A mixture melting point with the methyl ester obtained in (*a*) showed no depression.

(*c*) *From 2,2-isopropylidenebis[5-(dimethylfurfuryl)furan] and methyl levulinate in methanol.*—Treatment of a solution of 0.4 g. (0.001 mole) of 2,2-isopropylidene*bis*[5-(dimethylfurfuryl)furan] and 0.65 g. (0.005 mole) of methyl levulinate in 5 ml. of absolute methanol with anhydrous hydrogen chloride gas resulted in 0.17 g. (34%) of crude product, m.p. 155.5°–156.5°. Crystallization from methanol (35 ml./g.) gave 0.09 g. (18%) of white needles, m.p. 157.7°. A mixture melting point with the compound obtained in (*a*) showed no depression. When the above reaction (*c*) was carried out using ethanol as a solvent, the ethyl ester condensation product was obtained in 47% yield.

2,2-Difurylbutane

In a three-necked 2-liter flask, fitted with reflux condenser, mechanical stirrer, and dropping funnel, were placed 340 g. (5.0 moles) of furan, 150 ml. of commercial absolute ethanol, and 100 ml. of 37% hydrochloric acid solution. To this mixture was added dropwise, while stirring, 180 g. (2.5 moles) of butanone. The addition of butanone was complete after 60 minutes, during which time no heat was evolved and the reaction mixture had taken on a reddish tinge. When stirring was discontinued after 190 hours, the mixture separated into two phases. The lower dark orange organic phase was separated from the upper pink aqueous phase and washed with 5% sodium bicarbonate solution until neutral. It was then dried over anhydrous magnesium sulphate. After the excess furan and butanone were flashed off, the residual oil was fractionally distilled under reduced pressure.

The first fraction, a colorless oil, boiled at 64°–66° (1 mm.), and weighed 71 g. (15%).

2,5-Bis(ethylmethylfurfuryl)furan (III)

A second fraction from the preceding distillation was a pale yellowish-green oil boiling at 143°–145° (1 mm.). It weighed 168 g. (43%), η_D^{20} 1.5094, d_4^{20} 1.045. Anal. Calc. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.74; mol. wt., 312. Found: C, 76.6; H, 7.54; mol. wt., 327.

2,2-Butylidenebis[5-(ethylmethylfurfuryl)furan] (I; R = Me; R_1, R_2 = Et)

A third fraction from the preceding distillation, a viscous, fluorescent, yellow oil, boiled at 205°–210° (1 mm.). It weighed 82.8 g. (23%), η_D^{20} 1.5173, d_4^{20} 1.046. Anal. Calc. for $C_{28}H_{34}O_4$: C, 77.4; H, 7.89; mol. wt., 435. Found: C, 77.0; H, 7.79; mol. wt., 400.

2,7,12,17-Tetraethyl-2,7,12,17-tetramethyl-21,22,23,24-tetroxaquaterene (II; R = Me; R_1, R_2, R_3 = Et)

(*a*) *From 2,2-difurylbutane and butanone.*—The method of Ackman, Brown, and Wright (1) was used. A solution of 1.0 g. (0.0052 mole) of 2,2-difurylbutane and 3.0 g. (0.042 mole) of butanone in 10 ml. of absolute ethanol was saturated with anhydrous hydrogen chloride gas. Purification of the resulting solid resulted in 0.335 g. (27%) of white needles, m.p. 174°.

(*b*) *From 2,2-butylidenebis[5-(ethylmethylfurfuryl)furan] and butanone.*—A solution of 1.1 g. (0.025 mole) of I (R = Me; R_1, R_2 = Et) and 1.9 g. (0.025 mole) of butanone in 10 ml. of absolute ethanol was saturated with anhydrous chloride gas. The solution turned a deep cherry red and crystals began to form. On cooling, the mixture was filtered and the residue washed with 5 ml. of 95% ethanol to give 1.06 g. (87%) of light yellow needles, m.p. 169°–170°. Crystallization from absolute ethanol gave 0.78 g. (65%) of shiny white needles, m.p. 174°. A mixture melting point of this compound with the one obtained in (*a*) showed no depression.

ACKNOWLEDGMENTS

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THE MOLECULAR WEIGHT OF POLYVINYL ACETATE[1]

A. F. Sirianni, R. Tremblay,[2] and I. E. Puddington

ABSTRACT

The molecular weights of a series of unfractionated polyvinyl acetates of low degrees of polymerization have been measured by determining the lowering of the vapor pressure of their solutions. An approximate molecular-weight range of 5000–40,000 was examined. While most of the determinations were made in benzene solutions at 55° C., other solvents and temperatures were used. Anomalous results were obtained with one sample of fractionated material.

INTRODUCTION

A method for the determination of the molecular weights of chemical compounds based on measurements of the difference in vapor pressure between solutions of these compounds and the pure solvents has already been described (1). The previous publications dealt with the behavior of substances of known chemical constitution having molecular weights below about 1000 when examined in a variety of solvents and concentrations and over a range of temperatures.

The present communication describes results obtained with a series of commercial vinyl acetate polymers of comparatively low degree of polymerization. The individual samples, designated as Gelva 1.5, 2.5, 2.61, 7, 10, and 15, were obtained through the courtesy of Shawinigan Chemicals Ltd. The range of molecular weight covered by the series is approximately 5000 to 40,000. A single sample of fractionated polyvinyl acetate recovered from a solution was also examined.

APPARATUS AND EXPERIMENTAL

The apparatus and experimental technique have been described elsewhere (1). Molecular-weight determinations were usually carried out in benzene solution at 55° C. In some instances, however, other temperatures were used and a few determinations were made in acetone, methanol, and ethanol.

About 1 to 8 mg. of the dried polymer was weighed from the bulk sample into a 4 mm. i.d. pyrex tube and anchored to the bottom of the sample holder with a drop of distilled solvent. The occasional sample of polymer was prepared in powder form by freeze-drying its benzene solution. No difference in behavior during subsequent operations was found with samples prepared in this manner, however, and the simpler procedure was generally used. A metal stirrer about 1.5 cm. in length enclosed in a glass sheath was inserted into the tube containing the sample. The sample holder was sealed to the apparatus and the pressure reduced to about 10^{-5} mm. Hg. The apparatus was then flushed out with solvent vapor and re-evacuated. Solutions of various concentrations were prepared by condensing different amounts of solvent on the polymer sample. In this way a number of concentrations could be examined without opening the apparatus to the atmosphere. Differential vapor pressure measurements were normally begun after the solution had stood overnight with stirring. The reproducibility of these measurements was usually within 1%. The null point of the instrument was checked at the end of a series of measurements. Two or three different amounts of solute were used to obtain the entire concentration range studied.

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[2]*National Research Council Postdoctorate Fellow, 1954–56. Present address: Canadian Industries Limited, Beloeil, Quebec. Paper presented in part at the sixth Canadian High Polymer Forum, St. Catharines, Ontario, April 14–15, 1956.*

RESULTS

The variation of apparent molecular weight as a function of solution concentration for a series of Gelvas in benzene at 55° C. is shown in Fig. 1. The values for the molecular weight recorded here were calculated from Raoult's law. In addition to the determinations made in benzene, results obtained with Gelva 10 in absolute ethanol at 55° C., with Gelva 1.5 in acetone and in methanol at 20° C., and with Gelva 10 and Gelva 2.5 in benzene at 42.5° C. are shown in Fig. 2. In each case good agreement was obtained when the molecular-weight values were extrapolated to zero solute concentration.

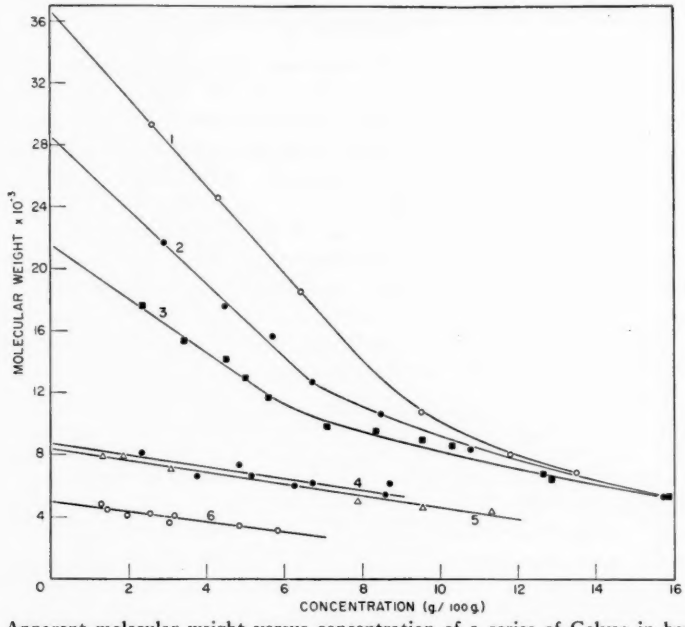

FIG. 1. Apparent molecular weight versus concentration of a series of Gelvas in benzene at 55° C. Curve 1, Gelva 15; Curve 2, Gelva 10; Curve 3, Gelva 7; Curve 4, Gelva 2.61; Curve 5, Gelva 2.5; Curve 6, Gelva 1.5.

It is evident that in most cases the apparent molecular weight is not a linear function of concentration. This is particularly obvious where the extrapolated molecular weight is in excess of 10,000. However, a straight line can be fitted reasonably well at lower concentrations, and where the molecular weight is below 10,000 the relation is quite linear up to 12% concentration.

In contrast to its behavior in benzene and in acetone, the measured molecular weight of Gelva 1.5 in absolute methanol appears to be independent of concentration over the range examined.

The behavior of the system Gelva 10 – ethanol is of considerable interest. The first determinations after fresh samples of solute were used produced a graph that was similar to that obtained with Gelva 1.5 in methanol. Subsequent determinations where the solvent was replaced by fresh ethanol gave a series of points where the molecular weight varies considerably with concentration. The extrapolated values in each case were virtually identical, however.

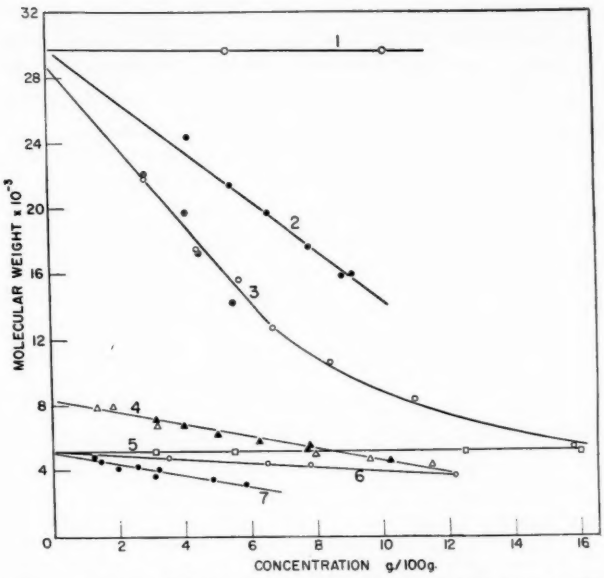

FIG. 2. Apparent molecular weight versus concentration of some Gelvas in different solvents and at various temperatures. Curve 1, Gelva 10, first determination in ethanol at 55° C.; Curve 2, Gelva 10, normal determination in ethanol at 55° C.; Curve 3, open circles, Gelva 10 in benzene at 55° C., and starred circles, at 42.5° C.; Curve 4, open triangles, Gelva 2.5 in benzene at 55° C., filled triangles, in benzene at 42.5° C., Curve 5, Gelva 1.5 in methanol at 20° C.; Curve 6, Gelva 1.5 in acetone at 20° C.; Curve 7, Gelva 1.5 in benzene at 20° C.

Since methanol is not a good solvent for polyvinyl acetate, the low degree of solute–solvent interaction may cause the solution of Gelva 1.5 to behave in the "ideal" fashion indicated. The similar behavior of fresh samples of Gelva 10 in ethanol might be ascribed to a trace of residual water in the resin which reduces solute–solvent interaction in the original solutions. If this were indeed the case, the water should be removed in subsequent operations and a higher solute–solvent interaction would be expected in succeeding solutions where the same sample of solute is used with fresh solvent.

In view of the departures of the apparent molecular weight vs. concentration curve from linearity in Fig. 1, it seemed of interest to apply an alternative method of presenting the vapor pressure data. The equation used, applicable over a wider range of concentrations provided μ_1 remains constant, is based on the theoretical equation developed by Huggins (2, 3) and by Flory (4, 5)

$$\phi \equiv (\ln a_1 - \ln V_1)/V_2 - 1 = -\bar{V}_1/\bar{V}_2 + \mu_1 V_2,$$

where

V_1, V_2 = volume fractions of components,
$\bar{V}_1$, $\bar{V}_2$ = partial molar volumes of components,
$\bar{V}_1 \simeq M_1/d_1$,
$\bar{V}_2 \simeq M_2/d_2$,
and a_1 = activity of the solvent;

M_1 and d_1, M_2 and d_2 are the molecular weight and density of the solvent and solute respectively.

A plot of ϕ vs. V_2 for the various polymers is shown in Fig. 3. In this case reasonably linear relations were found over the concentration range examined. The slopes of these graphs give the constant μ_1 directly and the molecular weight can be calculated from the intercept.

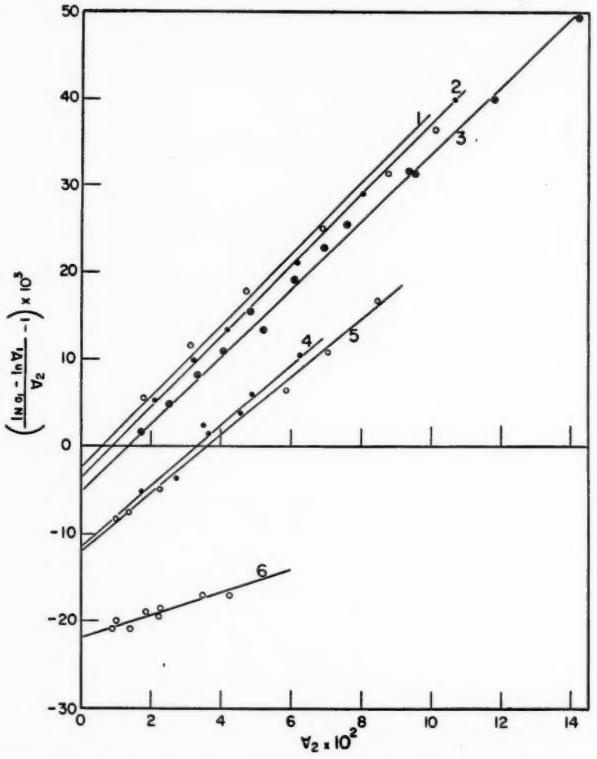

FIG. 3. Variation of $(\ln a_1 - \ln V_1)/V_2 - 1$ vs. V_2 for a series of Gelvas in benzene at 55° C. Curve 1, Gelva 15; Curve 2, Gelva 10; Curve 3, Gelva 7; Curve 4, Gelva 2.61; Curve 5, Gelva 2.5; Curve 6, Gelva 1.5.

The number-average molecular weight and the values of μ_1 for the series of Gelvas in benzene at 55° C. are given in Table I. Allowance for the non-ideal behavior of the solvent vapor has been made in calculating the concentration of the solutions. This correction amounted to about 2% on the molecular weight at infinite dilution.

TABLE I

MOLECULAR WEIGHTS OF POLYVINYL ACETATE IN BENZENE AT 55° C.

		Huggins' equation	
Gelva No.	M, Raoult's law	M	μ_1
1.5	5,100	4,960	0.134
2.5	8,500	9,010	0.333
2.61	9,000	9,560	0.347
7	22,000	21,800	0.387
10	28,600	30,300	0.401
15	36,700	45,400	0.402

In calculating the solution concentration, it was assumed that the volumes of solute and solvent are additive (6). The density of polyvinyl acetate was taken as 1.17 g./ml. for all of the fractions (7). The error involved by the change of density with molecular weight should not exceed 1%. The density of Gelva 0.9 at 20° C. has been reported as 1.159 g./ml. (8).

In addition to the work on the unfractionated polymers, several molecular-weight determinations were carried out on a sample of fractionated polyvinyl acetate made available to us through the kindness of Prof. M. Rinfret of the University of Montreal. When determined by a viscometric technique this sample had a weight-average molecular weight of 29,000. The polymer was recovered, after it had been stored for 6 months as an ethylene dichloride solution, by evaporation of the solvent under reduced pressure. It was then dissolved in benzene, filtered, and evaporated to a small volume. This concentrated solution was frozen and the solute was finally isolated as a fluffy brownish solid by subliming off the benzene.

Molecular weights were determined in ethanol and in benzene at 55° C. Two extra points were obtained in benzene solution at 65° C. The results, shown in Fig. 4, were calculated from Raoult's law.

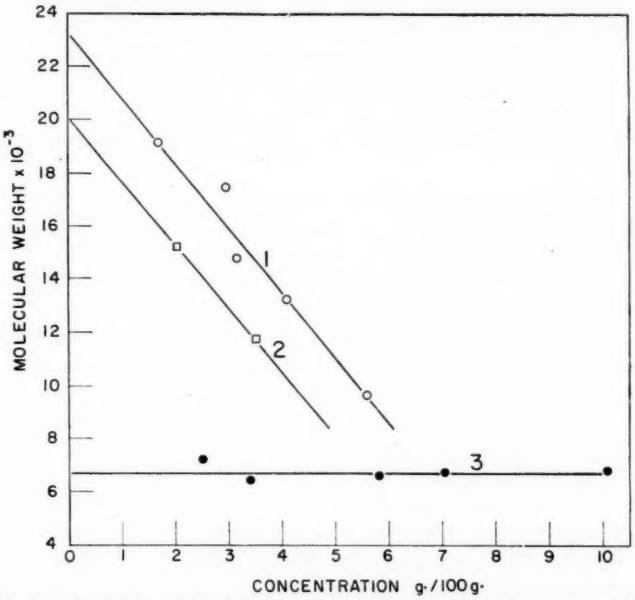

FIG. 4. Variation of apparent molecular weight versus concentration of a recovered fraction of polyvinyl acetate in benzene and in ethanol. Curve 1, in benzene at 55° C.; Curve 2, in benzene at 65° C.; Curve 3, in ethanol at 55° C.

The values obtained in ethanol solution were independent of concentration over the range used and were lower than expected. In benzene, although the molecular weight decreased as the temperature was raised from 55° C. to 65° C., the extrapolated value at both temperatures was much higher than in alcohol. While the reason for this difference is not obvious, it appears that the polymer may have become degraded during the long period of solution in the ethylene dichloride. The apparent difference in molecular weight in the polar and non-polar solvents might be ascribed to association of the solute

in the latter if any hydrolysis had occurred in the degraded polymer. Association phenomena have been observed (9, 10) with solutions of polymers containing a few hydroxyl groups in non-polar solvents and our results suggest the possibility of similar behavior. It may be added, however, that with unfractionated Gelva 10 and Gelva 2.5 there was virtually no difference in molecular weight when determinations were made in benzene at 42.5° C. and at 55° C.

DISCUSSION

The values of μ_1 are seen to decrease with decreasing molecular weight of the polymers in the series used. While this is sometimes attributed to solute impurities (3), the phenomenon has been observed for a series of polystyrene fractions in different solvents (11). Flory (12) suggested that μ_1 should be slightly dependent on molecular weight. The possibility that the variation of μ_1 with molecular weight is caused by chain branching (13) in the commercial samples (14) should not be excluded.

The values of the number-average molecular weights obtained using Raoult's law agree reasonably well with those found with Huggins' equation (2, 3) in spite of the fact that the values estimated by the latter method are very sensitive to slight changes in the slope of the curve and that rather long and possibly uncertain extrapolations were required using Raoult's law. This probably accounts for the difference found in Table I when the values obtained by the two procedures are compared.

The vapor-pressure data may also be presented as corrected π/c vs. C plots. These have not been included however, since this relationship is linear over the concentration range examined for the three polymers of the group with the lowest molecular weights only.

It is difficult to check the vapor-pressure method by calibration with known compounds of similar molecular weight since for the samples used reliable values for the degrees of polymerization are not readily available. A molecular weight of 61,000 was reported for Gelva 15 by Robertson, McIntosh, and Grummitt (15). This value was obtained by osmotic-pressure measurements on a commercial sample that had been dissolved in acetone, filtered, and precipitated in water. Since only that portion of the polymer that gathered around the glass stirrer was recovered, this treatment may have resulted in the loss of some low-molecular-weight material, and the value of 37,000 for Gelva 15 obtained in this work is perhaps not unreasonable. The distribution curves for Gelva 15 and Gelva 2.5 obtained by Blease and Tuckett (16) lend support to the molecular-weight values found here.

In favor of the vapor-pressure method, it may be pointed out that good agreement was generally obtained for the same material with different solvents and very satisfactory results were produced with pure compounds having molecular weights below 1000. Its most obvious advantage over osmotic-pressure methods, particularly where the molecular weights of the solute involved are low, is in avoiding semipermeable membranes. Its applicability over a wide temperature range is also an attractive feature.

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METHYLATION OF SUGAR MERCAPTALS

I. INTRODUCTION AND D-GLUCOSE DIETHYL MERCAPTAL[1]

G. G. S. DUTTON AND K. YATES

ABSTRACT

The methylation of the diethyl mercaptals of D-glucose, D-mannose, D-galactose, and L-arabinose in methyl iodide has been re-examined. The apparent lack of reactivity of the last three has been shown to be due to their insolubility in methyl iodide since appreciable methylation occurs in tetrahydrofuran. The case of D-glucose diethyl mercaptal has been examined in some detail and although polysubstitution occurs on reaction with methyl iodide in tetrahydrofuran the only monomethyl derivative formed is the 2-*O*-methyl ether. Preliminary work suggests that this is not the case with D-mannose mercaptal.

The reactions of sugar mercaptals are of particular interest in that the sugar molecule is acyclic, thus exposing an extra hydroxyl group which in the more common glycoside structure is involved in ring formation. It was reported in 1934 by Lieser and Leckzyck (1) that D-glucose diethyl mercaptal could be selectively methylated by the use of methyl iodide and silver oxide at 0° C. to give exclusively 2-*O*-methyl-D-glucose diethyl mercaptal in 52% yield. This reaction affords an easy route to 2-*O*-methyl-D-glucose and has been used by other workers (2). It was also reported by Lieser and Leckzyck that the mercaptals of D-galactose, L-arabinose, D-xylose, and L-rhamnose failed to yield methylated products when treated similarly.

It seemed to us that there was no a priori reason why other mercaptals should not react like the glucose compound. We have, therefore, re-examined this reaction to determine its generality and with the hope that it might furnish a convenient route to other partly methylated sugars such as are needed when carrying out structural studies by the methylation technique. Apart from the practical significance of such a reaction the nature of the monomethyl sugars obtained has considerable theoretical interest with respect to a study of the relative reactivity of the hydroxyl groups in an acyclic sugar derivative.

The early literature on relative reactivities of hydroxyl groups in carbohydrates has been reviewed (3) but the great majority of the examples refer to cyclic sugar structures. In 1952 there appeared a paper (4) showing that hexitols adopt a planar zigzag form resulting in selectivity in certain reactions, and it is reasonable to suppose that in some respects the acyclic mercaptals may be compared to the polyols. More recently Zinner (5, 6) has shown that in partial esterification of sugar mercaptals the terminal or primary hydroxyl group is the most reactive.

The present paper describes the qualitative paper-chromatographic examination of the products obtained on methylating the diethyl mercaptals of D-galactose, D-mannose, D-glucose, and L-arabinose. The results of a larger-scale methylation of D-glucose diethyl mercaptal and the quantitative separation of the products by column chromatography are also given.

In the initial experiments small amounts of the above mercaptals were methylated by the method of Lieser and Leckzyck (1). Upon separation of the products from excess methyl iodide and silver oxide, sirups were obtained. The sirup from the reaction of

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D-glucose diethyl mercaptal crystallized spontaneously to give a 46% yield of 2-*O*-methyl-D-glucose diethyl mercaptal, the others failing to yield any crystalline material except unchanged mercaptal. The mother liquor from the 2-*O*-methyl-D-glucose mercaptal and the remaining three sirups were investigated by paper partition chromatography. On development of the chromatogram with iodine vapor (7), the presence of several components was indicated as shown in Table I, indicating qualitatively that the

TABLE I

R_x VALUES OF PRODUCTS OF METHYLATION OF MERCAPTALS IN METHYL IODIDE

D-Glucose		D-Mannose		D-Galactose		L-Arabinose	
R_x*	Description	R_x	Description	R_x	Description	R_x	Description
0.13	OF	0.10	OF	0.13	OF	0.13	OF
0.21	OF	0.18	OF	0.21	OF	0.21	OF
0.36	OI	0.36	OI	0.40	OI	0.40	OI
—		—		0.47	OF	0.46	OF
—		0.94†	YI	0.95†	YF	0.95†	YI
1.00	YI	1.07	YF	1.03	YI	1.05	YF

*R_x *is based on the arbitrary standard 2-O-methyl-*D*-glucose diethyl mercaptal = 1.00 (*n*-BuOH–EtOH–H_2O = 40–10–50).*

†*These values correspond to standards of the unsubstituted mercaptals.*

KEY.—O = *orange*, Y = *yellow*, I = *intense*, F = *faint*.

reaction is more general than had been supposed. The presence of a further amount of 2-*O*-methyl-D-glucose diethyl mercaptal in the mother liquor suggested that, if desired, the yield of this product could be increased to 52% as given by the earlier workers (1). It can be seen from Table I that the reaction in each case gave products of two types; those having a high R_f value corresponded to methylated and unchanged mercaptals, while those having slower R_f's are presumably more polar compounds whose constitution is at present unknown. The latter compounds are referred to subsequently as the "slow fraction". It can, however, be stated that in these slow-moving compounds the mercaptal group has not been removed completely since they gave no spot for reducing sugar with *p*-anisidine hydrochloride (8). It is also apparent that these compounds are probably carbohydrate in nature since their R_f values varied from sugar to sugar, but on hydrolysis with acid, however, they did not regenerate the parent sugars. It was observed that the most intense of these slow spots can be produced by reacting the mercaptal with methyl iodide in the absence of silver oxide.

From the distribution and concentration of the products in Table I it appears that the reaction has been most extensive in the case of D-glucose since no unchanged mercaptal was detected. Somewhat less reaction occurs in the case of D-galactose and only a small amount in the cases of the other two mercaptals. Owing to the high R_f values of the mercaptals and consequent low degree of chromatographic separation, the products were hydrolyzed and reinvestigated by paper chromatography as the free sugars thus produced. These results are shown in Table II. From a comparison with the characteristic R_f values of known compounds it appears that the first components (from the origin) correspond to unsubstituted sugars, the second to their monomethyl derivatives, and the remainder to more highly substituted sugars. From this it can be seen that some monomethylation has occurred in each case, which is in apparent disagreement with the earlier statement that the reaction failed for sugar mercaptals other than those of D-glucose (1). Since the amount of methylation which has apparently taken place in

the case of the D-mannose and L-arabinose mercaptals is very slight and considerable polymethylation has occurred with D-galactose mercaptal, it is not surprising that no crystalline methyl derivative was isolated (1).

TABLE II

R_G* VALUES OF HYDROLYZED PRODUCTS OF METHYLATIONS IN METHYL IODIDE

D-Glucose	D-Mannose	D-Galactose	L-Arabinose
—	0.11 I	0.08 F	0.12 I
0.23 I	0.28 F	0.22 F	0.34 F
—	—	0.39 F	—
—	—	0.72 F	—
—	—	0.86 F	—

*R_G values based on 2,3,4,6-tetra-O-methyl-D-glucose = 1.00 (n–BuOH–EtOH–H_2O = 40–10–50).

During this preliminary work it was observed that there were considerable differences in the solubilities of the various mercaptals in methyl iodide. Under the conditions used it was found that the extent of methylation corresponded approximately to the degree of solubility of the particular mercaptal being reacted. D-Glucose diethyl mercaptal was found to be the most soluble of the four and its unusual reactivity appears in part to be due to the fortuitous choice of methyl iodide as a reaction solvent. Large amounts of D-mannose and L-arabinose mercaptals were found undissolved at the end of the reaction.

In order to eliminate this solubility effect it was decided to use an inert reaction solvent in which all four mercaptals had comparable solubilities and to compare the reaction of each again on a more equal basis. The most suitable of the common organic solvents which are inert to methylation was found to be tetrahydrofuran. The presence of a large amount of inert solvent necessitated the use of increased amounts of methyl iodide and silver oxide. In order to determine whether changing the original reaction temperature of 0° C. had any critical effect on the nature of the products three parallel reactions were carried out on each mercaptal at 3°, 22°, and 50° C. In the case of all four mercaptals no significant difference could be detected either in the distribution or in the intensity of the components when the reaction mixtures were examined by paper chromatography. The results of a typical methylation in tetrahydrofuran are shown in Table III. It was noted that the same "slow" products were present and the extent

TABLE III

R_x* VALUES OF PRODUCTS OF METHYLATION OF MERCAPTALS IN TETRAHYDROFURAN

D-Glucose	D-Mannose	D-Galactose	L-Arabinose
0.10	0.10	0.13	0.13
0.20	0.18	0.21	0.21
0.36	0.36	0.39	0.40
0.95	0.96	0.96	— †
1.00	1.00	1.02	1.03

*2-O-Methyl-D-glucose diethyl mercaptal = 1.00 (n–BuOH–EtOH–H_2O = 40–10–50).

†The absence of a spot for unreacted mercaptal corresponding to the spots for L-arabinose produced on hydrolysis may be due to the greater sensitivity of p-anisidine.

of methylation appeared more comparable in each case. The unusual reactivity of D-glucose diethyl mercaptal was not now so marked since unreacted mercaptal was shown to be present. In order to investigate the nature of the methylated mercaptals these were hydrolyzed and examined as the free sugars. These results are shown in Table IV, from which it is apparent that some monomethylation has taken place in all cases and that D-glucose mercaptal no longer yields exclusively monomethyl products. From these preliminary experiments it was concluded that if the methylation was carried out in a solvent it was generally applicable to the four mercaptals used and that the peculiar selectivity of the D-glucose mercaptal was no longer apparent.

TABLE IV

R_G* VALUES OF HYDROLYZED PRODUCTS OF METHYLATIONS IN TETRAHYDROFURAN

D-Glucose	D-Mannose	D-Galactose	L-Arabinose
0.09	0.13	0.08	0.12
0.23	0.26	0.20	0.32
0.42	0.45	0.38	0.44
0.47			0.50
			0.64

*R_G values based on 2,3,4,6-tetra-O-methyl-D-glucose = 1.00 (n-BuOH–EtOH–H_2O = 40–10–50).

In the light of the above results it was decided to repeat the methylation of D-glucose diethyl mercaptal on a larger scale to permit separation and identification of the reaction products. We were particularly concerned with the identification of the monomethyl fraction in order to determine if monomethylation still occurred preferentially at the 2-position. For this reason no attempt has been made at the present time to identify more highly methylated derivatives.

A large-scale methylation of D-glucose diethyl mercaptal was carried out in tetrahydrofuran at 22° C. After removal of the solvent and excess reagents the sirupy reaction product was separated on a cellulose column into two fractions: the "fast" fraction containing methylated and unreacted mercaptals and the "slow" fraction containing the unidentified products. The "fast" fraction was then hydrolyzed and the mixture of free sugars separated by chromatography on a cellulose–hydrocellulose column (9). The results of this separation are shown in Table V and the monomethyl fraction was

TABLE V

SEPARATION OF D-GLUCOSE O-METHYL ETHERS ON CELLULOSE–HYDROCELLULOSE (1:1) COLUMN

Classification	Tube No.	Wt. (mg.)	$[\alpha]_D^{20}$	R_f*	% OCH_3†
Hexose	238–270	23	+48° (H_2O)	0.017	—
Monomethyl	169–235	104	+59° (H_2O)	0.05	15.7
Dimethyl A	57–74	50	+82° (acetone)	0.28	26.5
Dimethyl B	86–108	47	+32° (acetone)	0.18	24.8
Dimethyl C	30–40	42	+61° (MeOH)	0.47	27.3
Trimethyl A	28–29	11	+91° (MeOH)	0.50	36.6
Trimethyl B	12–19	63	+20° (H_2O)	0.80	36.6
	Total	340			
	Recovery	84%			

*R_f values determined in methyl ethyl ketone – water azeotrope.
†Calculated methoxyl values for mono-, di-, and tri-methyl hexoses respectively are 16.0, 29.7, and 41.9%.

shown to be one component by paper chromatography and the constancy of optical rotation throughout the fraction. This fraction crystallized spontaneously and failed to depress the melting point of an authentic sample of 2-*O*-methyl-D-glucose on admixture with it. It was further characterized by the preparation of the characteristic *p*-toluidide derivative. It was thus shown that although polymethylation occurs when D-glucose diethyl mercaptal is reacted with methyl iodide in a solvent it is only the 2-monomethyl ether that is formed, thus demonstrating the superior reactivity of the 2-position.

When a large-scale methylation of D-mannose diethyl mercaptal was carried out under identical conditions two principal monomethyl derivatives were produced and these appeared to be the 5-*O*- and 6-*O*-methyl-D-mannoses. In the case of L-arabinose mercaptal, under these conditions mainly di- and tri-methylation occurred. These results and those on D-galactose mercaptal will be reported more fully at a later date.

EXPERIMENTAL

All melting points were taken by means of a Leitz electrically heated melting-point block and are corrected. All evaporations were done *in vacuo* at 40° C. Duolite A_4 anion-exchange resin is a product of Chemical Process Co., Redwood City, California.

Preparation of Diethyl Mercaptals

The four mercaptals were prepared by the method of Fischer (10) and had melting points and rotations in agreement with those given. The rotations of D-mannose diethyl mercaptal and of L-arabinose diethyl mercaptal do not appear to have been previously recorded and were found to be $[\alpha]_D^{20} = 0°$ (*c*, 0.77 in pyridine) and $-5°$ (*c*, 1.78 in pyridine).

Methylation of Mercaptals in Methyl Iodide (1)

D-Glucose diethyl mercaptal (0.94 g.) was shaken with freshly prepared silver oxide (1.5 g.) and methyl iodide (10 ml.) for 21 hours at 0° C. under anhydrous conditions. The mixture was allowed to attain room temperature (1 hour) and filtered. The residue was extracted successively with boiling chloroform, acetone, and methanol. The filtrate and extracts were combined and evaporated to a sirup, which was dissolved in a small amount of methanol. On standing, this solution deposited crystals (0.46 g.) of 2-*O*-methyl-D-glucose diethyl mercaptal, m.p. 154°–155° C. Lit. m.p. 155°–156° C. (1). Anal.: Calc. for $C_{11}H_{24}O_5S_2$: $—OCH_3 = 10.37\%$. Found: $—OCH_3 = 10.99\%$. Yield 46%.

The diethyl mercaptals of D-mannose, D-galactose, and L-arabinose were also methylated by the above procedure but the sirups obtained failed to yield any crystalline product.

Chromatographic Investigation of the Reaction Products

Chromatograms of the four reaction products above were run on Whatman No. 1 paper, using *n*-butanol–ethanol–water (40:10:50). Detection of the chromatograms with iodine vapor (5) showed the components whose R_x values are given in Table I. Duplicate chromatograms were sprayed with *p*-anisidine hydrochloride but failed to detect any reducing sugars (8).

Effect of Individual Reagents

Two samples of D-glucose diethyl mercaptal (10 mg.) were dissolved in carbon tetrachloride (5 ml.) and shaken for 21 hours at 0° C. with methyl iodide and silver oxide respectively. After they were filtered, the solutions were chromatographed with standards and detected as before. Mercaptal plus methyl iodide: three products of $R_x = 0.21, 0.35$

(intense), and 0.94 (unchanged mercaptal). Mercaptal plus silver oxide: one product of $R_x = 0.95$ (unchanged mercaptal).

Hydrolysis of Reaction Products

The sirups resulting from methylation of the four mercaptals were dissolved in 20% aqueous ethanol containing 5% hydrogen chloride. The solution was heated to reflux, a stream of nitrogen being bubbled through continuously. When chromatography of the solutions failed to detect any unchanged mercaptals (5 to 6 hours), they were passed through a column of Duolite A-4 anion-exchange resin and concentrated by evaporation. The four hydrolyzates were chromatographed on paper as before and detected with *p*-anisidine hydrochloride, the results being shown in Table II.

Methylation of Mercaptals in Tetrahydrofuran

The mercaptal (0.3 g.) was dissolved in dry peroxide-free tetrahydrofuran (20 ml.). After silver oxide (1 g.) and methyl iodide (10 ml.) were added, the whole was shaken vigorously for 22 hours. Three parallel experiments were carried out on each mercaptal at 3°, 22°, and 50° C. The products were then extracted as before, no crystalline materials being obtained. Paper chromatography of the sirups as before yielded results shown in Table III. After hydrolysis and chromatography of the free sugars the results shown in Table IV were obtained.

Large-Scale Methylation of D-*Glucose Diethyl Mercaptal*

Silver oxide (6.7 g.) and methyl iodide (67 ml.) were added to a solution of D-glucose diethyl mercaptal (2.0 g.) in purified tetrahydrofuran (100 ml.). The vessel was flushed with nitrogen, sealed, and shaken at room temperature for 22 hours. After extraction of the products there was obtained an amber sirup (2.07 g.). Paper chromatography of this sirup using methyl ethyl ketone – water azeotrope gave essentially the same results as shown in Table III. Part of the sirup (1.96 g.) was placed on a cellulose column (2.8 cm. diam. by 40 cm.) and developed with the same solvent. Fractions were collected at 1-hour intervals for 8 hours. (The time for the solvent front to pass down the column was 4 hours as judged by the addition of Sudan IV dye.) Two fractions were then collected at 2-hour intervals and the remaining material was removed by developing for a further 80 hours without any attempt at fractionation. Paper chromatographic examination of the first eight fractions in methyl ethyl ketone – water and detection with iodine vapor showed that fractions 2–5 contained all of the mercaptalated products with only slight traces of the "slow" fraction. When these fractions were combined and the solvent evaporated there was obtained a sirup (0.88 g.) designated as mercaptal fraction. The higher fractions were discarded.

The mercaptal fraction was hydrolyzed as before and yielded a sirup (0.425 g.). Duplicate chromatograms of the sirup were run in methyl ethyl ketone – water. One chromatogram was exposed to iodine vapor and the other sprayed with *p*-anisidine hydrochloride. The former showed no glucose mercaptal, indicating that hydrolysis was complete. The latter showed four components with R_f's 0.014, 0.06, 0.21, and 0.47, corresponding to the characteristic ranges of glucose and mono-, di-, and tri-methyl glucoses respectively.

A portion of the sirup (0.406 g.) in the minimum amount of methyl ethyl ketone was placed on a column (2.8×42 cm.) of cellulose–hydrocellulose (1:1) and developed with methyl ethyl ketone – water azeotrope. Fractions were collected at 30-minute intervals at a flow rate of 40 ml. per hour. After 300 fractions had been collected no

further carbohydrate material could be detected (Molisch). The results of this fractionation are shown in Table V.

All the fractions were found to be chromatographically pure except for some overlap between dimethyl glucose fractions A and B. By evaporation of the solvent from a few tubes from the beginning, middle, and end of the monomethyl fraction it was shown to have a constant rotation throughout. This monomethyl fraction yielded spontaneously, a crystalline product melting at 153°–157° C. After recrystallization, admixture with an authentic sample of 2-*O*-methyl-D-glucose gave a melting point of 154°–158° C. (2). The *p*-toluidide was prepared in poor yield by the method of Smith (11), m.p. 144°–146° C. Lit. m.p. 150°–151° C. (12).

It will be noted from Table V that the methoxyl analysis of the separate fractions is in some cases much lower than is demanded by theory. This is attributed to the difficulty of purifying small amounts of sirup from inert material from the column (cellulose?). The main significance of the methoxyl analyses was to indicate that the other components were not monomethyl glucoses.

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THE THERMODYNAMICS OF MUTAROTATION OF SOME SUGARS

I. MEASUREMENT OF THE HEAT OF MUTAROTATION BY MICROCALORIMETRY[1]

M. A. KABAYAMA, D. PATTERSON, AND L. PICHE

ABSTRACT

The heats of mutarotation of D-glucose, D-xylose, lactose, maltose, and cellobiose have been determined using a microcalorimeter of the Tian-Calvet type. Part I of this paper describes the experimental work and the results obtained. Discussion of these results is reserved for Part II.

INTRODUCTION

Since the discovery of the phenomenon of mutarotation, much work has been done to elucidate the kinetics and mechanism of the reaction as well as to study the stability of the various forms postulated. Some attempt has also been made to determine the heats of mutarotation of the sugars from the temperature dependence of the equilibrium constants for the mutarotations (1). The only direct measurement of a heat of mutarotation has been performed by Sturtevant (2, 3) for D-glucose using an adiabatic calorimeter. It seemed desirable, however, to have values for other sugars, particularly for those undergoing an opposing first-order mutarotation, in order to make a comparison of the appropriate thermodynamic quantities.

MATERIALS

The sugars studied were all of reagent grade purity, and were obtained as almost pure α or β anomers by slow recrystallization from slightly supersaturated aqueous or alcoholic solutions according to the method of Hudson and Dale (4).

The "purity", i.e. the percentage of α or β anomer in the "α" or "β" sugar, may be determined polarimetrically using known optical rotations. These experiments were performed at 0° C. Isbell and Pigman (5) have determined the optical rotations at 0° C. for both anomers of D-glucose and lactose and for α-D-xylose and β-maltose. They have also obtained a value at this temperature for β-cellobiose (6). The optical rotations at 20° C. for the other anomers required have been obtained by Hudson and Yanovsky (7) using an indirect method requiring the separation of only one of the anomers of the sugar. Their values have been used to find the "purity" of the sugars at 0° C. Since the "purities" of the sugars, save for cellobiose, were nearly 100%, this introduces a negligible uncertainty. In the case of cellobiose, the "purity" was sufficiently far from 100% to warrant a polarimetric run at a higher temperature.

The water used in all experiments was ordinary distilled water, saturated with CO_2, and of pH approximately 5.5. Since the rate of mutarotation of D-glucose is constant (8) between pH 2 and 7, buffering of the solution (8, 9) was deemed unnecessary for a determination of the heats of mutarotation.

EXPERIMENTAL

The Tian-Calvet microcalorimeter has been described in various publications (10, 11, 12), but an outline of its more relevant characteristics will be given here. Although arranged differentially, it consists essentially of a cell in which the reaction takes place

[1]*Manuscript received November 12, 1957.*
Contribution from the Department of Chemistry, University of Montreal, Montreal, Que.

and a block whose temperature remains constant. The temperature difference between the cell and the block is detected by a set of thermocouples and galvanometer and recorded by a photopen on a chart.

However, the heat evolved by the reaction only in part raises the temperature of the cell producing the deflection recorded on the chart. The rest of the heat is conducted down the thermocouples to the block. Nevertheless, the rate of evolution of heat is related to the deflection and the time rate of change of the deflection by the following equation:

$$W(t) = \frac{p}{g}\delta + \frac{\mu}{g}\frac{d\delta}{dt}. \qquad [1]$$

Here $W(t)$ is the rate of evolution of heat in joules/second, p is the rate of thermal conduction of heat down the thermocouples per degree temperature difference between the cell and the block, δ is the deflection on the chart in cm., g is the sensitivity of the thermocouples, galvanometer, and photopen in cm. deflection per deg. temperature difference between cell and block.

Equation [1] may be expressed as:

$$W(t) = \frac{p}{g}\Delta, \qquad [2]$$

where

$$\Delta = \delta + \frac{\mu}{p}\frac{d\delta}{dt} \qquad [3]$$

and is a "corrected" deflection related to $W(t)$ by a constant, p/g.

In the present case, the large heat of solution of the sugar had to be separated from the much smaller heat of mutarotation. This was effected by determining the evolution of heat some time after the dissolution of the sugar when the heat was due to the mutarotation alone; by extrapolation to zero time, the whole heat of mutarotation was determined. Thus, using [3], Δ was obtained graphically from the curve of the deflection δ against time commencing some 30 minutes after dissolution of the sugar. The mutarotations studied are all single first-order opposing reactions; a curve of log Δ against time was extrapolated back to zero time in an appropriate fashion, and the intercept of log Δ on the axis $t = 0$ gave the log of the total heat evolved by the mutarotation. Since the "purity" of the sample was slightly less than 100%, a correction to 100% purity was then made.

Prior to the experiment, the sugar was held in a special holder (Fig. 1) within the stainless steel reaction cell of the microcalorimeter. The holder was designed to give a low heat effect on opening. After the tension of the spring (not shown) was released, the bracket was lowered via the control wire. The hook in the center engaged the shaft to suspend the holder so that the water was allowed to circulate through the top and bottom of the cylinder to dissolve the sugar. The endothermic heat of solution was compensated by evolution of heat from a resistor within the cell in order to allow the microcalorimeter to be put as quickly as possible onto its maximum sensitivity. This was required for following the evolution of the small heat of mutarotation.

The heat of mutarotation of a sugar possessing a fast rate constant, D-lyxose, and a check on the value of D-xylose, was obtained by the so-called "ballistic" method. Dissolution of a sugar gives an immediate "ballistic" deflection on the chart which quickly

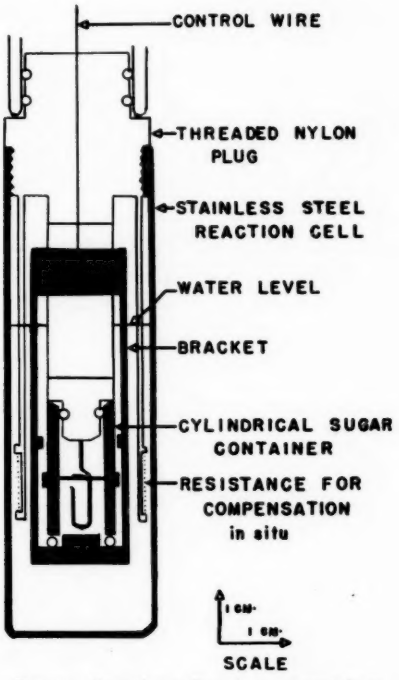

FIG. 1. Reaction cell and sugar container.

reaches a maximum and then slowly falls off. This peak deflection is almost entirely due to the heat of solution and is proportional to it. By measuring the height of the peak for the dissolution of KNO_3, whose heat of solution is well known, the instrument may be calibrated. Thus the heat of solution of the sugar may be determined. Measurement of the total area under the curve of deflection vs. time gives the heat of solution plus the heat of mutarotation. By subtracting the heat of solution, the heat of mutarotation may be obtained separately. Owing to the small size of the difference, the precision of this method is not high.

RESULTS

A typical curve of deflection vs. time as recorded on the chart is displayed in Fig. 2, with the curve of Δ against time as found by using equation [2]. A plot of $1+\log \Delta$ against time is shown in Fig. 3 with an extrapolation to zero time.

The second column of Table I shows the heat of mutarotation found for the various sugars on the basis of total conversion of the sugar from the α to the β anomer. The precision attained in the calorimetric determinations is indicated by the second number in this column. In the fourth column, the percentage β in the equilibrium mixture is found, these values (except for a small correction) having been drawn from the references cited above (5, 6, 7), which are valid at 20° C. The correction is necessary because of the temperature difference, and has been made using the Gibbs–Helmholtz equation and the experimentally determined heats of mutarotation. By the use of well-known thermodynamic relations, values of ΔF and ΔS may be found, and these are given in columns five and six. Fig. 4 presents a plot of ΔH vs. ΔS.

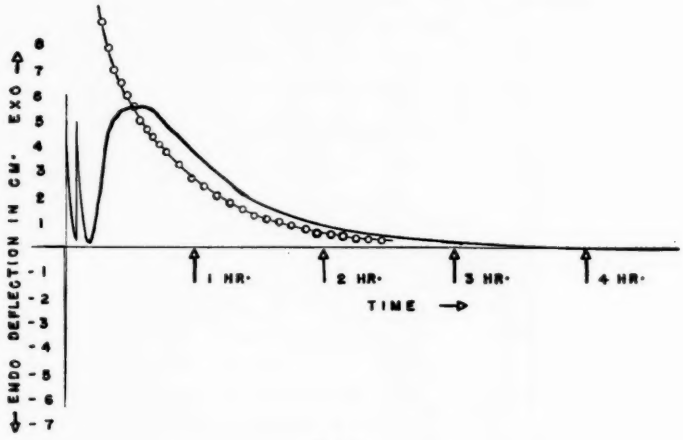

FIG. 2.

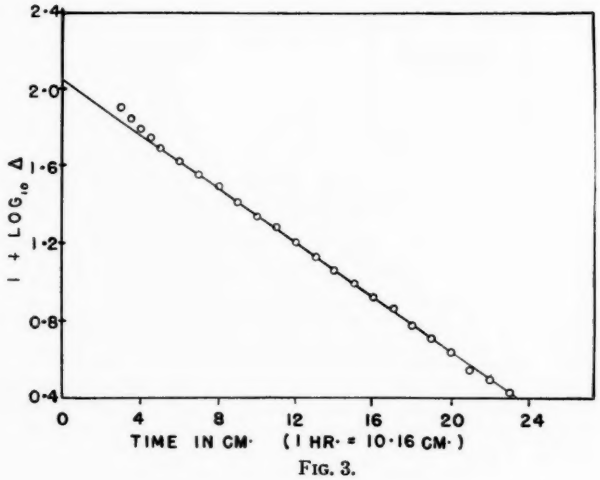

FIG. 3.

TABLE I

Sugar	ΔH, cal./deg.-mole, precision in %	Starting form	% β at 24.8° C.	ΔF, cal./mole	ΔS, e.u.	k_1+k_2, min.$^{-1}$, precision in %
D-Xylose	−535 ±3.9	α	65.5	−379	−0.52	0.038 ±10
Cellobiose	−438 ±2.0	β	64.4	−352	−0.29	0.0053 ± 2
D-Glucose	−270 ±1.4	α	63.6	−327	+0.19	0.0112 ± 4
Lactose.H_2O	−270 ±1.4	α	62.3	−297	+0.08	0.0070 ± 7
Maltose.H_2O	−126 ±7.3	β	63.9	−335	+0.70	0.0090 ±11

The accuracy of the work, as distinct from the precision, is more difficult to assess. For D-glucose and lactose, since the initial rotations of both anomers of the sugars have been determined accurately by Isbell and Pigman (5, 6), the percentage composition

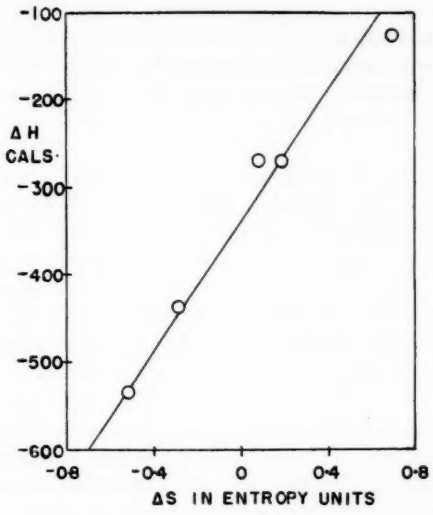

FIG. 4.

of the equilibrium solution is also known, so that the error in the values of the thermodynamic quantities should be of the order of the precision found. In fact, the value of ΔH for D-glucose agrees within 3% with that obtained by Sturtevant, viz., 277.7 cal./mole. However, in the case of the three other sugars, we are forced to rely upon the approximate values of Hudson and Yanovsky for one of the initial rotations. From a discussion of the possible uncertainty in these values, we conclude that in the case of maltose, the following limits are not unreasonable: for ΔH, $\pm 4\%$, ΔF, $\pm 10\%$, and for ΔS, $\pm 20\%$. The large relative error in the last value is due to the small value of ΔS. This introduces an uncertainty in the absolute value of 0.1 e.u. For D-xylose and cellobiose, these limits would be less.

The "ballistic" method gave a value of the heat of mutarotation of D-xylose equal to -460 cal./mole, which provides only a rough check of the value in Table I since the precision of the "ballistic" method is estimated to be $\pm 28\%$. The value obtained for D-xylose was $+312$ cal./mole with a similar precision. The positive value of ΔH is no doubt due to the axial hydrogen on $C_{(2)}$ which renders the β anomer energetically unfavored; ΔF for the mutarotation is now positive and the equilibrium composition of the sugar is 24.8% β at 25° C.

It is also possible to obtain the rate constant of the mutarotation from the slope of log $W(t)$ plotted against the time, hence from the slope of the straight line in Fig. 2. The values of k_1+k_2, the rate constant of the reaction, are shown in the last column of Table I, with the variation which was found for a series of four to seven experimental runs. The rather large variation found here seems also to occur amongst values in the literature. Isbell and Pigman (6) point out that the mutarotation is sensitive to the presence of certain metals, and it is possible that in our case, the reaction was catalyzed to some extent by brass which might have shown through the rhodium plating of the holder for the sugar. Since, however, we are interested in the heat of mutarotation between equilibrium states, any change in the rate of the reaction should not affect the thermodynamic values obtained.

The values of k_1+k_2 found by Isbell and Pigman (6) at 0° C. and 20° C. have been extrapolated to yield the following values at 24.8° C.: D-glucose, 0.0102 min.$^{-1}$; lactose.H_2O, 0.0076 min.$^{-1}$; D-xylose, 0.0381 min.$^{-1}$; maltose.H_2O, 0.0086 min.$^{-1}$. The agreement is thus seen to be satisfactory in view of the variations found.

DISCUSSION

We may note that the value of ΔH obtained for D-glucose agrees reasonably well with that obtained by Sturtevant (6), namely -278 cal./mole at 25° C.

Apart from D-lyxose, the sugars studied are identical in the neighborhood of the anomeric carbon. It is therefore surprising to find the large range of values for ΔH and ΔS shown in Table I. This is particularly so since ΔF is nearly constant for these sugars; this latter fact is reflected in the straight line obtained in Fig. 4.

A detailed discussion of these results is presented in Part II of this paper.

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THE THERMODYNAMICS OF MUTAROTATION OF SOME SUGARS

II. THEORETICAL CONSIDERATIONS[1]

M. A. KABAYAMA AND D. PATTERSON

ABSTRACT

An interpretation of ΔH and ΔS for the mutarotation of D-glucose, D-xylose, maltose, lactose, and cellobiose is given in terms of changes in the hydration of the reducing hydroxyl group.

INTRODUCTION

In this part of the paper we shall attempt to give an interpretation of the experimental results shown in Table I and Fig. 4 of Part I.* We shall first consider the conformations of the sugars used in Part I and note that in all of them the neighboring groups of the reducing carbon are identical.

There is a large body of evidence for strong hydrogen bonding between the sugar hydroxyl groups and adjacent water molecules in aqueous solution. On the basis of the known conformations of the sugars and of the structure of water it is possible to come to tentative conclusions about the packing of the water molecules about the sugar molecule, and to predict that an equatorial hydroxyl group will be more strongly hydrated than an axial group. We also find that the reducing hydroxyl of the sugars of Part I is bonded to the adjacent water molecule in the same manner, with only slight variations in bond length.

The large value of ΔS for mutarotation of the various sugars can be associated with changes in the frequency of torsional oscillation of this reducing hydroxyl group about the $C_{(1)}$—O axis. On the basis of a simple model of the hydrogen bond between the group and the water molecule, the order of magnitude of this frequency can be calculated and shown to be low enough to give a large contribution to the entropy.

Using the hydrogen bond model, the order of magnitude of the variation of ΔS and ΔH amongst the sugars is calculated, and the slope of ΔH vs. ΔS in Fig. 4 of Part I can be estimated theoretically.

Finally ΔF for the mutarotation of the sugars can be viewed in the light of the free energies of interaction between adjacent hydroxyl groups in the cyclitols which have been the subject of thermodynamic study by Angyal and McHugh (1). Because the pyranose ring contains an oxygen atom, whereas the cyclitol ring does not, a difference exists between group interactions in the two cases.

CONFORMATIONS OF THE SUGARS

Reeves (2) has shown that of the two chair and six boat conformations possible for the hexopyranoses the chair conformations are normally preferred. More recent work in Reeves' laboratory (3, 4) has indicated the possibility of a boat conformation in some of the pyranoses, the tendency of hydroxyl groups to take up equatorial positions apparently overcoming the normal stereochemical preference for the chair conformation.

[1]*Manuscript received November 12, 1957.*
Contribution from the Department of Chemistry, University of Montreal, Montreal, Que.
**Preceding paper.*

D-Glucose and D-xylose, however, retain the normal C1 conformation shown for β-glucose in Fig. 1. This conformation has been confirmed by X-ray diffraction evidence for cellulose (5) and methyl β-D-xyloside (6, quoted in 5).

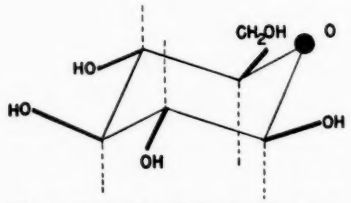

FIG. 1. The conformation of the β-D-glucose molecule.

In the disaccharides, there is no reason to suppose that the β-D-(1→4)-linked glucose residues of cellobiose are not both in the conformation found for solid cellulose. In the case of lactose, 4-*O*-(β-D-galactopyranosyl)-D-glucose, there is some evidence from X-ray diffraction work on the solid (7) that the galactose residue is distorted from the C1 conformation because of the axial OH on $C_{(4)}$ to produce a flatter molecule than would otherwise be the case. Reeves and Blouin (4) also suggest that the axial hydroxyl in galactose tends to become more equatorial distorting the C1 conformation.

The presence of a boat conformation in maltose and amylose seems to be indicated (3). Haworth (8) originally predicted that the α-D-(1→4)-linked glucose residues of amylose would lie in a boat conformation. Reeves has shown that they take up either of two boat conformations which put the α-D-(1→4) linkages in equatorial positions. Maltose, however, does not seem to have the same extent of boat conformation. Here the only steric requirement is that the 1-hydroxyl on the glycosidic residue and the 4-hydroxyl on the reducing residue be in equatorial positions to make the 1→4 linkage equatorial. This requirement is satisfied if the glycosidic residue is in a boat conformation (actually, most likely the B1), leaving the reducing glucose residue in the C1 conformation. This structure is in accord with the resemblance of the mutarotation thermodynamics of maltose to that of the other sugars shown in Fig. 4 of Part I. Such would not be the case were the reducing residue in maltose also in a boat conformation.

SOLVATION OF THE SUGARS

(*a*) *Evidence for Hydration*

Thermodynamic studies of glucose and sucrose in aqueous solution (9) show that they must be extensively hydrated, presumably by hydrogen bonding between the hydroxyl groups and the water molecules. Evidence from the intrinsic viscosities of aqueous solutions of D-glucose and sucrose shows that the van der Waals volume of these molecules is increased by a factor of about two by hydration (10).

The distances between adjacent hydroxyl groups in the pyranose ring are almost identical with those in the 1,2-cyclohexanediols. There, intramolecular hydrogen bonds can exist when the molecules are in CCl_4 solution (11), and result in decreases of the hydroxyl stretching frequency equal to 32 $cm.^{-1}$ when both hydroxyls are equatorial, and equal to 39 $cm.^{-1}$ when one is equatorial and the other axial. It is apparent from the smallness of these shifts that the intramolecular bonds are very weak. It is therefore highly probable that in aqueous solution, the sugar hydroxyls are directed outwards to oxygen atoms of adjacent water molecules, thus destroying the intramolecular hydrogen bonding between hydroxyls.

If, however, intramolecular hydrogen bonding is preserved by sugar molecules in solution, the hydroxyl stretching-frequency shift should be of the order of that observed for the 1,2-cyclohexanediols in CCl_4. On the other hand, if the hydroxyls form strong hydrogen bonds with the water oxygens, frequency shifts of several hundred cm.$^{-1}$ might be expected.

Some infrared spectroscopic observations seem pertinent to this subject, and they also give evidence of intermolecular association between sugar molecules. A Perkin-Elmer model 112 spectrometer with a NaCl prism was used to obtain spectra of a 0.1 *M* solution of α-D-glucose in pyridine and of 0.1 *M*, 0.01 *M*, and 0.002 *M* solutions of α-D-xylose in pyridine. The hydroxyl stretching-frequency band of α-D-glucose had a peak about 3250 cm.$^{-1}$ compared with the free hydroxyl value of about 3625 cm.$^{-1}$. With increasing dilution, the peak of the band for D-xylose moved from about 3300 cm.$^{-1}$ to about 3400 cm.$^{-1}$, presumably showing the effect of an association between the sugar molecules.

Since the mutarotation experiments were performed with concentrations of the order of 0.2 *M*, we must conclude that some intermolecular interaction occurred. The same may be said of the experiments of Sturtevant (12), who used concentrations of 0.15–0.3 *M* D-glucose. At low concentrations when intermolecular association was greatly reduced, the hydroxyl stretching frequency still seems too low (~3400 cm.$^{-1}$) for it to be due to intramolecularly bonded hydroxyl groups. It appears that hydroxyl groups of the sugar molecules form hydrogen bonds with the ring nitrogens of the pyridine molecules, rather than remaining intramolecularly bonded. Similarly, in water, the relatively weak intramolecular hydrogen bonds are in all probability replaced by strong bonds with the oxygen atoms of surrounding water molecules.

(*b*) *The Water Structure*

In water, the oxygen atom of each molecule is tetrahedrally coordinated by means of hydrogen bonds to the oxygen atoms of adjacent water molecules, the water structure thus resembling the SiO_2 structure. Bernal and Fowler (13) proposed the rather open tridymite SiO_2 structure for ice, and the closer-packed but still four-coordinated quartz SiO_2 structure for water at normal temperatures. X-Ray diffraction work by Morgan and Warren (14) has shown that the assumption of a quartz structure for water must be modified slightly. Recently, Pople (15) proposed a continuation of the tridymite ice structure with increasing bending of the hydrogen bonds and a movement of molecules into formerly unoccupied regions of the open ice structure.

Fig. 2(*a*) shows a plane of oxygen atoms of water molecules in the tridymite structure (16), as viewed along the hexagonal axis, each hydrogen bond between adjacent oxygen atoms containing a hydrogen atom which is not shown. The hexagons are skew and are all in the chair conformation. The atoms of the plane are repeated directly above and below those shown, but the chairs are rotated through 60°, so that atoms below the median plane of the chair are now above, and vice versa. In Fig. 2(*a*), the atoms marked ▽ and △ are joined by straight hydrogen bonds to the atoms directly above and below, respectively. In the adjacent planes above and below, the corresponding atoms would be marked △ and ▽ with the convention referred to above. The tridymite structure appears in Fig. 2(*b*) as seen from the side.

(*c*) *Hydration of the Monosaccharides*

In discussing hydration of the sugar molecules, we shall take the tridymite structure as a model for water, thus neglecting bending of the hydrogen bonds and the accompanying molecular disorder. The dimension marked on Fig. 2(*a*) for the O—O distance (2.90 Å) was found by Morgan and Warren (14) for water just above 0° C.

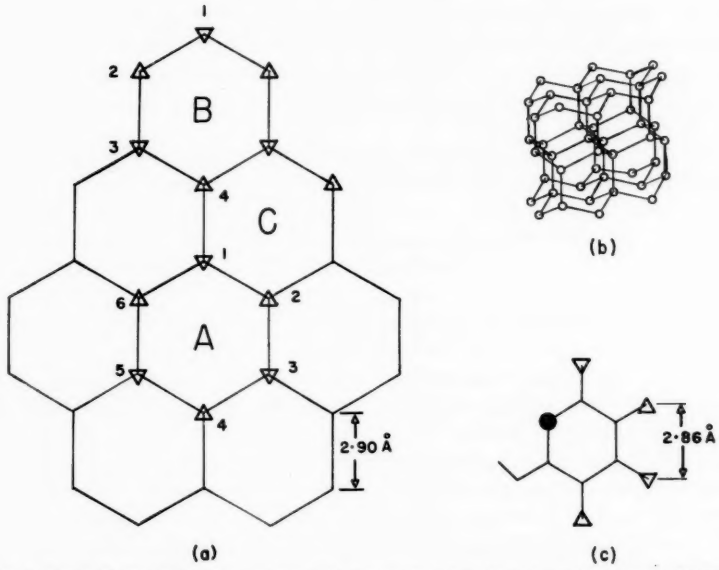

FIG. 2. (*a*) A plane of the tridymite structure in water showing direction of H bonds. (*b*) The tridymite structure. (*c*) The D-glucose molecule showing direction of possible perpendicular H bonds.

Fig. 2(*c*) shows the β-D-glucose molecule from above. The triangles mark the oxygens of hydroxyl groups on $C_{(1)}$ to $C_{(4)}$. Assuming the chair form of Fig. 1 for the β-D-glucose ring, one finds that the hydrogens of these hydroxyl groups may be placed directly above (▽) or directly below (△) the oxygens, and are thus capable of forming hydrogen bonds in these directions in a manner similar to that of the oxygen atoms in the water structure. Furthermore, the distance between adjacent oxygens of the D-glucose hydroxyls (2.86 Å) is almost identical with that between adjacent oxygens in water (2.90 Å).

It is thus apparent that the D-glucose molecule can replace a chair conformation of water oxygens in Fig. 2(*a*), e.g. the hexagon A. The oxygens on $C_{(1)}$ to $C_{(4)}$ replace oxygens marked 1 to 4 forming strong hydrogen bonds with water oxygens in planes above and below; the only distortion involved is the replacement of a hexagon of side 2.90 Å by one of side 2.86 Å. It may be seen from a model that the primary hydroxyl group on $C_{(6)}$ may form a bent hydrogen bond with an adjacent oxygen of a water molecule in the same plane as the sugar molecule. Finally, the "lone-pair" orbitals of the ring oxygen found near position 6 lie in the direction of the hydrogen atom on the adjacent oxygen in the same plane.

There is a second mode of hydration which might also occur. This involves bonding of the equatorial hydroxyls to adjacent water molecule oxygens in the same plane rather than in planes above and below. In order to do this, the molecule must be flattened as if a conformational inversion were taking place.

It seems difficult to choose between these two modes of hydration for equatorial hydroxyl groups. The energy necessary to flatten the ring would seem to favor the first mode of hydration. There seems, however, to be some evidence (17) that the glucose ring consists of five carbon atoms more or less in a plane, with an oxygen atom out of the plane, rather than the skew hexagon of the cyclohexane ring. In this case, the second mode of hydration would probably be favored.

On the other hand, if we have an axial hydroxyl, inspection of a model shows that hydrogen bonding may take place only with the oxygens of water molecules adjacent to the sugar and in the same plane. A considerably bent H bond is the result, and at the same time a partial inversion of the conformation must take place; because of the bent bond, we conclude that the hydration of an axial hydroxyl group is considerably less than that of an equatorial hydroxyl of a chair conformation. This is in conformity with the preference (as found by Reeves) of the sugars to assume those conformations having equatorial hydroxyls.

The hydration of D-xylose should take place in essentially the same manner as that outlined above for D-glucose.

(*d*) *Solvation of the Disaccharides*

The structure of the cellobiose molecule in the solid is shown from above in Fig. 3(*a*), and is identical with that of any two adjacent units of the cellulose chain (17). The C—O—C valence bond angle of the glycosidic linkage lies in the plane perpendicular to that of the paper so that the linkage appears straight. Haworth (8) originally proposed the structure of Fig. 3(*b*) as the unit of the cellulose chain. The C—O—C valence angle now lies in the plane of the paper and one residue has rotated 60° from position B to C. (In Fig. 3(*a*) appropriate bond distances are foreshortened to allow for the C—O—C valence angle.) It is interesting to note that the over-all lengths of these two different conformations are the same, viz. 10.3 Å. The triangles again show the relative directions of the hydrogen bonds, which can be directed in perpendicular directions.

A consideration of steric interferences in atomic models has led Hermans and his collaborators (18) to propose the cellobiose molecule of Fig. 3(*b*) as a unit of the cellulose chain. More recently, X-ray diffraction work (19) suggests this unit for the cellulose II (mercerized cellulose) chain while the unit of Fig. 3(*a*) is retained for cellulose I (native cellulose).

There are two reasons for supposing that, when the cellobiose molecule is in aqueous solution, the structure of Fig. 3(*a*) may transform itself into that of Fig. 3(*b*). Firstly, in order to fit the two D-glucose residues into the water lattice in the extended form, we

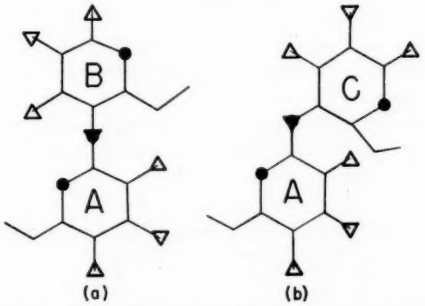

FIG. 3. Two conformations of the cellobiose molecule.

must identify the residues with the two hexagons of Fig. 2(*a*) marked A and B. In A, oxygens on $C_{(2)}$ to $C_{(4)}$ fall on points 2 to 4, and in B, oxygens on $C_{(1)}$ to $C_{(3)}$ fall on points 1 to 3. However, as shown by the positions of the triangles, the hydroxyls in D-glucose residue B cannot form hydrogen bonds in the directions required by hexagon B of the water lattice. The second point is that the over-all length of hexagons A and B in the water lattice is ~12.2 Å, whereas the corresponding cellobiose length is 10.3 Å;

this discrepancy would appear to be rather large and would result in greatly decreased hydration.

In the structure of Fig. 3(*b*), however, both residues will fit into the water lattice. Having rotated the residue B through 60° to position C, the hydrogen bonds now fit with those of hexagon C in the water lattice. Furthermore, the dimensions are such as to allow the molecule to take the place of the two adjacent hexagons A and C in the water structure without undue distortion.

As a result of these considerations, it seems likely that the cellobiose molecule takes up Haworth's Fig. 3(*b*) conformation in aqueous solution rather than retaining the conformation followed by the solid (Fig. 3(*a*)).

Presumably the same point of view will hold good for lactose. As previously mentioned, there is some evidence of distortion of the C1 galactose conformation owing to the axial 4-hydroxyl, possibly to increase hydration. This might also exist in the galactose residue in lactose.

The structure of maltose in solution may be deduced from that of amylose in solution. Haworth (8) originally proposed a conformation for amylose analogous to that which he suggested for cellulose. It is capable of forming spiral structures (20) whose dimensions have been verified by X-ray diffraction measurements on the amylose–iodine complex (21). Fig. 4 shows two units of the chain. The residue to the right must be considered to be in a boat conformation. While the dimensions of the molecule are appropriate for fitting it into the water structure, consideration of the model shows that, owing to the boat conformation, at least one of the hydrogen bonds formed by the right-hand residue must be somewhat bent. One might therefore expect that hydration of maltose would be less than that of other sugars.

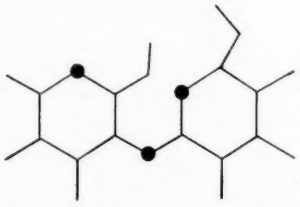

FIG. 4. The structure of the maltose molecule in solution.

As a result of the foregoing discussion of hydration, it seems likely that the packing of water molecules about the reducing hydroxyls will be much the same in D-glucose, D-xylose, cellobiose, lactose, and maltose. We have already noted the similarity of the conformations of these sugars. It thus appears that the differences in the thermodynamics of mutarotation presented in Part I must be due to rather small perturbations in the neighborhoods of the reducing carbons of these sugars.

THERMODYNAMICS OF MUTAROTATION

The negative ΔH for mutarotation of the sugars in Table I of Part I is in accord with the greater hydration for equatorial hydroxyl groups than for axial groups. Some of the values of ΔS are positive while others are negative; most would seem to be rather large as has been pointed out in Part I. Furthermore, the variation in ΔS amongst the sugars studied seems extremely large since the nearest neighbors of the reducing carbon are the same throughout, the conformations of the reducing residue being the same, in spite of small distortions of the molecules induced by the hydration. We shall first

develop a model to show that the large ΔS values are reasonable, and then use the model to discuss the relation between ΔH and ΔS manifested in Fig. 4 of Part I.

(a) The Magnitude of the Entropy Change

The entropy of a single vibrational mode is given (22) by

$$S = k\left[\frac{x}{e^x-1} - \ln(1-e^{-x})\right], \qquad x = h\nu/kT, \tag{1}$$

where ν is the vibrational frequency,
k is Boltzmann's constant, and
h is Planck's constant.

ΔS for the mutarotation is thus given by a summation of terms as in [1] if the change of vibrational frequencies upon mutarotation is known. It seems natural to suppose ΔS to result from the changing of frequency in a relatively small number of modes per molecule. For instance, Barker, Bourne, Stacey, and Whiffen (23) have demonstrated the existence of small characteristic differences between the spectra of α and β anomers of D-pyranoses in the region of 730–960 cm.$^{-1}$. Consideration of [1] shows, however, that the contribution of a vibrational mode to the entropy diminishes with increasing frequency so that frequency changes in the above region produce a negligible contribution to the entropy change. The largest change of frequency mentioned by Barker and collaborators produces a change of about 0.032 e.u. One must therefore seek the basis of the large ΔS values in a low-frequency vibrational mode, which is thus likely to be associated with a torsional oscillation rather than a bond bending vibration. The torsional oscillation of the OH group about the $C_{(1)}$—O bond would seem to be an attractive possibility. The torsional oscillation of the free hydroxyl in CH_3OH vapor (24) was found to have a mean frequency of 225 cm.$^{-1}$. With the formation of the hydrogen bond in the liquid phase of CH_3OH, the hydroxyl oscillation gives a very wide band centering about 650 cm.$^{-1}$ (25). In the case of a sugar hydroxyl hydrogen-bonded to a water molecule, the shift in the hydroxyl stretching frequency is rather less ($\sim$200 cm.$^{-1}$) than in the case of the hydroxyl in polymeric liquid methanol (301 cm.$^{-1}$(11)).

It is therefore reasonable to suppose a smaller energy for the hydrogen bond in the D-glucose hydration case than in liquid methanol. Hence one might expect an OH torsional frequency between 225 cm.$^{-1}$ and 650 cm.$^{-1}$, and thus of the order of magnitude required to give the ΔS values found. (A torsional frequency of 400 cm.$^{-1}$ gives a contribution to the entropy, following [1], of $\sim$1 e.u.)

(b) Model of the Hydrogen Bond

The following simple model of the hydrogen bond between the reducing hydroxyl and an adjacent water oxygen atom may be used to determine the order of magnitude of the hydroxyl's frequency of torsional oscillation. We assume electrostatic forces between point charges of magnitude $-q$ and $+q$ at the O and H of the reducing hydroxyl group and a charge $-2q$ at the O of the adjacent water molecule, as shown in Fig. 5. For the simple calculation which follows, we neglect the effect of $C_{(1)}$ and the ring on

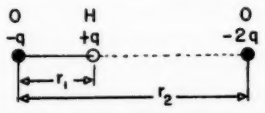

FIG. 5. Simple model of the hydrogen bond.

the charges of the hydroxyl oxygen and hydrogen. A repulsive Born–Mayer interaction also exists between the hydroxyl H and the water oxygen. This adds a term A/r^n to the energy. Verwey (26) in his simplified treatment of the hydrogen bond in water takes $n = 12$. Allowing the hydroxyl group to make small oscillations through an angle ϕ about an axis through its oxygen and perpendicular to the O—H direction, we find the torsional force constant:

$$g = [\partial^2 E/\partial\phi^2]_{\phi=0},$$

where E is the energy of the system. In this way,

$$[2] \qquad g = \frac{2q^2 r_1 r_2}{(r_2-r_1)^3}\left[1-\left\{\frac{An}{2(r_2-r_1)q^2}\right\}^{n-1}\right].$$

$(An/2q^2)^{n-1}$ has the dimensions of a (length)$^{n-1}$, or R^{n-1}. R has the physical significance of being the distance between the hydrogen and the water oxygen at which the repulsive force between these two atoms balances the attractive force. Then [2] becomes

$$[3] \qquad g = \frac{2q^2 r_1 r_2}{(r_2-r_1)^3}\left[1-\left\{\frac{R}{(r_2-r_1)}\right\}^{n-1}\right],$$

and the frequency is given by

$$\frac{1}{\lambda} = \frac{1}{2\pi c}\sqrt{\frac{g}{I}},$$

where I is the moment of inertia of the hydroxyl group about its axis of rotation. The energy of the hydrogen bond may be written as:

$$[4] \qquad E = -2q^2\left[\frac{1}{(r_2-r_1)}\left\{1-\left(\frac{1}{n}\right)\left(\frac{R}{r_2-r_1}\right)^{n-1}\right\}-\frac{1}{r_2}\right].$$

We take $q = 1.51\times10^{-10}$ e.s.u., chosen to give a dipole moment of 1.86 D. to the water molecule,

$$r_1 = 0.96 \text{ Å},$$
$$r_2 = 2.90 \text{ Å},$$
$$I = 1.236\times10^{-40} \text{ g-cm.}^2 \text{ (Ref. 24).}$$

From the relation of ΔH to ΔS (Fig. 4, Part I), it will be found that $[R/(r_2-r_1)]^{n-1} \sim 0.7$. Using these values in [3], g becomes 5.63×10^{-13} ergs and the frequency of torsional oscillation of the OH group is 360 cm.$^{-1}$, which seems very reasonable when compared with the OH torsional frequency of methanol. The energy of the hydrogen bond between the hydroxyl group and the oxygen atom of the adjacent water molecule is ~9.7 kcal./mole, which must be considered rather high. The effect of $C_{(1)}$ would be to raise the negative charge of the hydroxyl oxygen above that assigned to it here, and therefore to lower the energy of the hydrogen bond. A more detailed calculation does not appear warranted, however, since only orders of magnitude are sought.

THE RELATION BETWEEN ΔH AND ΔS

We shall assume that ΔH and ΔS change from sugar to sugar in Fig. 4 of Part I by reason of slight perturbations in the surroundings of the reducing hydroxyl which change the length of the hydrogen bond between the hydroxyl and the adjacent water molecule. This in turn is manifested in small changes in the enthalpy and entropy of either or

both of the α and β anomers, causing a variation of ΔH and ΔS between the sugars. Furthermore, we shall use the simple model of the hydrogen bond developed above for both anomers of the sugars. Thus, supposing slight changes $\Delta r_2'$ and $\Delta r_2''$ in the lengths of the hydrogen bonds in the α and β anomers respectively, the changes in ΔH and ΔS are given by:

$$\delta\,\Delta H \simeq \left(\frac{\partial E}{\partial r_2}\right)(\Delta r_2'' - \Delta r_2') \equiv \frac{\partial E}{\partial r_2}\,\Delta r_2,$$

$$\delta\,\Delta S \simeq \left(\frac{\partial S}{\partial r_2}\right)(\Delta r_2'' - \Delta r_2') \equiv \frac{\partial S}{\partial r_2}\,\Delta r_2.$$

Here E and S are given by expressions [4] and [1] respectively. Thus,

$$\delta\,\Delta H = \frac{2q^2}{(r_2-r_1)^2}\left[1-\left(\frac{R}{r_2-r_1}\right)^{n-1}-\left(\frac{r_2-r_1}{r_2}\right)^2\right]\Delta r_2 \qquad [5]$$

and

$$\frac{\delta\,\Delta S}{R} = -\frac{x^2e^x}{(e^x-1)^2}\,\frac{1}{2g}\,\frac{\partial g}{\partial r_2}\,\Delta r_2. \qquad [6]$$

In [6], using [3], and deriving g with respect to r_2, we have

$$\frac{\delta\,\Delta S}{R} = -\frac{x^2e^x}{2(e^x-1)^2}\left[\frac{1}{r_2}\left\{1-\frac{3r_2}{r_2-r_1}\right\}+\frac{[(n-1)/(r_2-r_1)][R/(r_2-r_1)]^{n-1}}{1-[R/(r_2-r_1)]^{n-1}}\right]\Delta r_2. \qquad [7]$$

Using the previously given values of the various quantities and with $[R/(r_2-r_1)]^{n-1} = 0.7$, we find $\Delta H = -2790 r_2$ cal./mole with r_2 in Å. Thus, a change of 0.1 Å produces 279 cal./mole change in ΔH. Correspondingly, $\delta\,\Delta S/R = -4.76\ \Delta r_2$ where r_2 is in Å. For $\Delta r_2 = 0.1$ Å, $\delta\,\Delta S = 0.946$ e.u. Furthermore, the slope of the line in Fig. 4 of Part I is given by

$$\mathscr{E}^* = \frac{\delta\,\Delta H}{\delta\,\Delta S/R} = 580 \text{ cal./mole.}$$

Although this figure is lower than the experimental value of 741 cal./mole, the agreement must be considered satisfactory considering the simplicity of the model. The value of $\mathscr{E}^*$ is not sensitive to the choice of $[R/(r_2-r_1)]^{n-1}$. When $[R/(r_2-r_1)]^{n-1} = 0.45$, the electrostatic attraction H . . . . . $O_{(2)}$ balances the $O_{(1)}$—$O_{(2)}$ electrostatic repulsion plus the Born–Mayer repulsion. Here $\delta\,\Delta H = 0$, and $\mathscr{E}^* = 0$. With our choice of $[R/(r_2-r_1)]^{n-1}$, we are assuming that the OH and the water oxygen are pushed slightly nearer together than this equilibrium distance.

STERIC INTERACTIONS IN THE PYRANOSE RING

Finally a word must be said about the steric interactions in the pyranose ring. Eliel and Lukach (27) have recently obtained a value for the free energy change for $OH_a \rightarrow OH_e$, and have made a comparison with other values available in the literature. There is a rather wide spread of these values, and the authors suggest a possible effect of the solvent used. Of the values mentioned, probably only that found by Angyal and McHugh (1) is relevant here, since although cyclitols rather than pyranoses were studied, their experiments were carried out in aqueous solution.

We notice that for all of the sugars in Table I of Part I, $\Delta F \sim 0.33$ kcal./mole. In each of these sugars the reducing residue is in the C1 conformation, and the change from

the α to the β anomer breaks two OH_a: H_a interactions and replaces an OH_e: OH_e interaction by an OH_e: OH_a interaction within the molecule. To a first approximation, these last two interactions may be taken as equal. At the same time, an axial group has become equatorial, changing the hydration energy of the molecule in aqueous solution. Thus, the total change of free energy may be written:

$$E - A - 2(OH_a: H_a) = 0.33 \text{ kcal./mole},$$

where E is the hydration free energy of an equatorial OH,
A is the hydration free energy of an axial OH,
OH_a: H_a is the free energy for formation of an OH_a: H_a interaction.

Thus OH_a: $H_a + \frac{1}{2}(A-E) = 0.17$ kcal./mole.

Angyal and McHugh have not taken account of hydration of the cyclitol hydroxyls explicitly. Nevertheless, of one allows for this effect, it is found that their interaction free-energy OH_a: H_a becomes OH_a: $H_a + \frac{1}{2}(A-E) = 0.45$ kcal./mole.

Thus a discrepancy exists between the two values. A tentative explanation may be advanced.

In the pyranose ring, the ring oxygen has four unpaired electrons located in two "lone-pair" orbitals on the upper side of the ring oxygen in Fig. 1. These would repel the corresponding "lone-pair" orbitals of the $C_{(1)}$ hydroxyl, and one might expect that the α anomer would be preferred to the β anomer. Such an effect has been mentioned by Edward (28). The size of the effect obviously depends on the orientation of the hydroxyl group in the α and β anomers, and hence on the manner of hydration. Two possible modes of hydration of the OH in the β anomer were considered above. It is interesting to note that the effect hardly exists for one mode of hydration, that where the hydroxyl forms a hydrogen bond with the plane of water molecules above the plane of the sugar molecule. With the other mode of hydration, that in which the hydrogen bond is directed to a water molecule in the same plane as the sugar molecule, the effect would be important Here, the lone-pair orbitals of the ring oxygen and the hydroxyl oxygen are considerably closer together in the β anomer than in the α anomer.

We may note also that the other interaction free-energies of the OH groups in the cyclitols as found by Angyal and McHugh are an indication of hydration of the cyclitols.

The interactions OH_a : OH_a and OH_e: OH_e† are found to have free energies of formation of 1.9 kcal./mole and 0.35 kcal./mole (13) respectively. In the cyclohexanediols in CCl_4, however, Kuhn finds intramolecular hydrogen bonding between pairs of OH groups and particularly in the OH_a: OH_a case. If this intramolecular hydrogen bonding were to exist for the cyclitols in aqueous solution, one would expect negative free-energies. On the other hand, hydrogen bonding of the hydroxyls to water molecules would break the intramoleculr hydrogen, turning the hydrogens of the hydroxyls outward. This would allow the "lone-pair" orbitals of the hydroxyl oxygens to interact and thus contribute towards a positive ΔF.

It may be further shown that if hydration is allowed for, we have OH_a: $OH_a + (A-E) = 1.9$ kcal./mole,

$$OH_e: OH_e = 0.35 \text{ kcal./mole}.$$

Thus, in the case of interaction between two axial hydroxyls the essentially positive

†*Angyal and McHugh do not differentiate between* OH_e : OH_e *and* OH_a : OH_e. *However, they appear to have actually found* ΔF *for* OH_e : OH_e *interactions, the other type of interaction cancelling out of the calculation.*

term $(A-E)$ also contributes to the high positive values for the total interaction free-energy.

ACKNOWLEDGMENTS

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SOME ANOMALOUS ELECTRICAL POLARIZATIONS[1]

PETER PODLESCHKA, LISELOTTE WESTLAND, AND GEORGE F WRIGHT

ABSTRACT

Dielectric-constant determinations of a series of solids previously reported to have high atom polarizations have not confirmed earlier opinions. Moreover, when it has been practicable to determine the change in polarization with respect to temperature, the relationship is not invariant. This variation may be, and in some instances should be, interpreted as evidence for orientation polarization. However, all such assignments cannot be certain until the change in solid dielectric constant with respect to temperature has been studied.

INTRODUCTION

This report is a continuation of recent (1) work showing that many electrical polarizations formerly attributed entirely to distortion polarization seem instead to have a component of orientation polarization in an applied field of about 1 electrostatic volt at 500 kc. These reassignments were based on dielectric constants of thin pellets pressed to maximum density from randomly oriented powders and were confirmed by determinations of the dielectric constants in benzene solutions at several temperatures. The present results, shown in Table I, also have previously been assigned abnormally high atom polarizations in lieu of orientation polarizations. These assignments seem to have been made in deference to current organic chemical theory or by analogy with another substance of the same class. It is evident from the data of Table I that the earlier opinions require revision. Each item will be discussed in order of appearance in the table.

TABLE I

DIELECTRIC CONSTANTS OF SOME SOLIDS AND SOLUTIONS IN BENZENE

Substance	d^{20}	ϵ, solid	Solution: Temp., °C.	$\Delta\epsilon/\Delta\omega$	$\Delta V/\Delta\omega$	P_T, cc.	P_{e+a}, cc.	P_e,* cc.	μ, D.
p,p'-Dicyanobiphenyl	1.267	3.244					68.9	61.1	
Tetramethylcyclobutanedione	1.167	2.406				47–48*	38.3	37.7	0.8*
p-Dinitrobenzene	1.617	2.887	20	0.62	0.469	53.0	40.1	38.5	0.78
			30	0.54	0.472	51.1			0.74
			40	0.48	0.477	49.7			0.69
Thorium acetylacetonate	1.753	3.056	20	0.56	0.555	175.1	145.7†	127.5	1.18
			30	0.74	0.560	198.6			1.61
			40	0.94	0.572	224.3			2.00
Zirconium acetylacetonate	1.412	2.952	20	1.08	0.385	207.6	136.0†	123.5	1.85
			30	1.28	0.411	225.5			2.10
			40	1.43	0.457	236.8			2.26

Quoted from pertinent literature (4, 5).
†*These pellets contain 2% of Koroseal.*

p,p'-Dicyanobiphenyl

In our earlier publication we doubted that the total polarization of 4,4′-dinitrobiphenyl in benzene could be due to electronic plus atomic polarization alone, because our distortion-polarization determination was only 0.8 cc. more than a reasonable value for electronic polarization. Moreover, our total polarization in benzene was about 10 cc.

[1]*Manuscript received November 20, 1957.*
Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario.

lower at 40° than that found by LeFevre and Vine (2) at 25°. The latter criterion of orientation polarization may be questionable because of the low solubility at 25°. For the same reason we would not rely on the total polarization value for the dicyano analogue in benzene, either as it was reported by LeFevre and Vine (at 25°) or on our own attempt to get a meaningful value at 40°. Therefore we cannot affirm that *p,p'*-dicyanobiphenyl has an orientation polarization. But we can say that the distortion polarization of 68.9 cc. which we found by capacitance measurements on the pelleted solid can account for only 68.9 − 61.1 = 7.8 cc. of atom polarization, in contrast to the larger value (35 cc.) previously assigned (3).

Tetramethylcyclobutanedione

The total polarization of this substance has been reported as 46.9 cc. in the vapor phase (4) and 48.5 cc. in benzene (5). Since the electronic-polarization value calculated from the latest bond constants (6) accounts for only 37.4 cc., our distortion polarization, determined experimentally, would include only 0.9 cc. of atom polarization. Thus there remains about 9 cc. of polarization indicative of a low orientation polarization for this supposedly rigid molecular structure.

p-Dinitrobenzene

The dielectric constant of pellets of this substance shows that the distortion polarization is 40.1 cc., or 1.6–1.9 cc. higher than the electronic polarization calculated from group-refractions. This directly determined atom polarization is somewhat lower than that postulated (4) previously (8.2 cc.). In order to confirm our result we have determined the polarization in benzene solution at 20°, 30°, and 40° C. We find (Table I and Fig. 1) that the total polarization does vary appreciably with temperature, as would be expected if it included a component of orientation polarization. Although this interpretation is contrary to that of Coop and Sutton (4) the experimental work may not be in disagreement. From the curvature of the plot of total polarization versus the reciprocal of absolute temperature (Fig. 1) it might be expected that the polarization at 200°–255° C. would be close to the 46.5 cc. that Coop and Sutton observed in their vapor phase study.

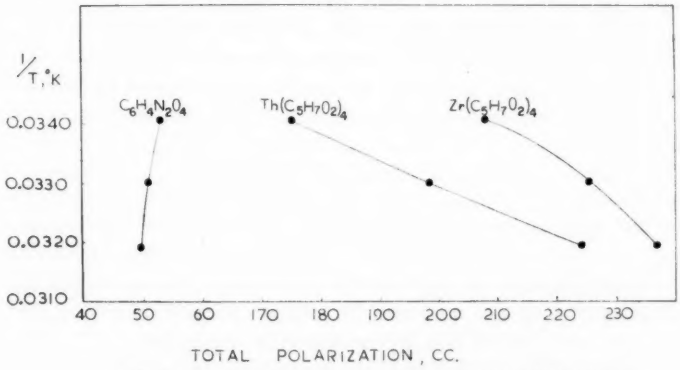

FIG. 1. Temperature coefficient of electrical polarization.

Agreement between our results and those of LeFevre and LeFevre is not as satisfactory. These workers found approximately the same polarization (46 cc.) in benzene at 25° and 45°, whereas in our apparatus (in which benzene solutions of naphthalene give

polarizations of 46.5 cc. for the latter substance both at 20° and 40°) the polarization of *p*-dinitrobenzene in benzene varies from 53.0 to 49.7 cc. over the 20° temperature range. The only difference (aside from the method of computation) apparent to us is the higher purity (m.p. 177.5°–178°) of our sublimed dinitrobenzene over that (m.p. 171°–172°) used by the earlier workers. Of course the greater precision due to improvements in electrical circuitry since 1935 may be contributory.

At any rate our results compel us to an assignment of a small but significant moment for *p*-dinitrobenzene which varies from 0.78 debye to 0.69 debye over our 20° temperature range. Since the moment decreases with increasing temperature it is unlikely to be due to out-of-plane bending of the nitro groups because of thermal agitation in a normally planar structure.

Indeed there is evidence that *p*-dinitrobenzene is normally not completely coplanar (7, 8). These structure analyses by X-ray diffraction have designated an angle of 11° 42′ between the planes of the nitro group and the benzene ring in an otherwise symmetrical molecule, but the electron density maps do not actually confirm the postulation of a centrosymmetrical molecule. In point of fact the possibility of accumulated errors (angle error ±2%) makes the X-ray diffraction study of limited value as a criterion of the out-of-plane atom distribution, which could account for the observed temperature-dependent polarization (9).

Metal Acetonylacetates

Two of these organometallic compounds have been studied. The polarizations found for thorium acetylacetonate at 20° and 30° in benzene fall in line approximately with the polarization in this solvent observed previously at 25° (10). The trend in our polarization data at 20°, 30°, and 40° is in disagreement with the previously determined vapor phase measurement, but observable decomposition (4) renders the latter observations unreliable. Of interest is the large temperature coefficient (Table I and Fig. 1) which we have observed in benzene solution. This evidence for appreciable orientation polarization (1.18–2.00 debyes from 20° to 40°) is confirmed by a separate determination of the dielectric constant of randomly distributed solid thorium acetylacetonate. Comparison of P_{e+a} (145.7 cc.) derived by this method with the P_e (127.5 cc.) calculated from refractive indices of benzene solutions (7) shows an atom polarization (P_A = 18.2 cc.) not very different from that reported for beryllium acetylacetonate (P_A = 21.2 cc.). The latter substance is the only one of the metal chelates with which a temperature–polarization study has previously been made, and the data showed that it had no permanent dipole moment (7).

Comparisons like these above are unsatisfactory in the case of zirconium tetraacetylacetonate. From the dielectric constant of the randomly oriented solid a distortion polarization (P_{e+a} = 136.0 cc.) has been calculated which is only 12.5 cc. greater than the electronic polarization calculated by Finn, Hampson, and Sutton (10). However, we are reluctant to compare any of our data for zirconium acetylacetonate with theirs. One cannot tell from the report by these authors whether their sample was pure. Neither melting point, density, nor analysis is mentioned so it is uncertain whether their sample was completely anhydrous. We have found the melting point (11) to be an unreliable criterion, but analysis for carbon, hydrogen, and water shows that our sample is pure within the limits of precision for these determinations.

The purity of our sample is important because our total solute polarizations of zirconium acetylacetonate (Table I) at 20° and 30° are both higher than that reported

(7) at 25°. Reference to Fig. 1 shows that the polarization increases markedly with increasing temperature. The line drawn through these polarization values differs from that for the thorium analogue because it is curved. This curvature might suggest a limiting temperature at which polarization is invariant.

One may be inclined to interpret these temperature-variable polarizations entirely in terms of dipole moment, but at present there is no justification for this simple interpretation. It seemed reasonable to us when we designated the temperature-dependent polarization of ferric acetylacetonate entirely in terms of dipole moment (1) because it decreased as temperature increased. Of course the opposite effect for thorium and zirconium acetylacetonates does not exclude the possiblity that these substances have dipole moments which increase because of less intramolecular hindrance at higher temperatures. In short the thorium and zirconium acetylacetonates might resemble a sterically hindered compound like 1,2-dichloroethane (3, p. 281). But also temperature-variation of atom polarization might occur as it does in substances like barium titanate (12). Such behavior would not be unexpected in these metal chelates, the molecular character of which need not entirely obliterate some salt-like properties.

It might have been expected that we would test the latter postulation by examination of the dielectric constants of the solids at different temperatures. Unfortunately we have not yet been able to devise a proper instrument for this purpose. An ultimate decision concerning the temperature-variable polarizations of thorium and zirconium acetylacetonates must await the successful construction of such apparatus.

The authors wish to thank P. Cooper, W. Boos, and M. Malaiyandi for experimental aid. The investigation could not have been made without generous financial support by the National Research Council of Canada. Mr. C. C. Meredith has given valuable advice.

EXPERIMENTAL*

Purification of Materials

The solvents used for dielectric-constant studies were purified and maintained as was described previously (1). Dicyanobiphenyl, prepared according to Ferris and Turner (13), was obtained in 70% yield, m.p. 185°–220°. After crystallization from pyridine, acetic acid, pyridine, and dioxane (m.p. 228°–232°, 39% of crude) the substance was sublimed at 180°–190° (20 mm., m.p. 232°–235°) and then crystallized (Darco) from ethanol (75 ml. per g.) to melt at 236°–237.5°. Tetramethylcyclobutanedione, synthesized from isobutyroyl chloride and triethylamine (14), was purified by repeated crystallization from benzene and finally by sublimation at 95° (750 mm.) during 4 days, repeated until a melting point of 114°–114.4° was attained. Dinitrobenzene (E.K. White Label) was sublimed repeatedly at 150°–160° (750 mm.) until it melted at 177.5°–178°. Thorium acetylacetonate (15) was crystallized from ethanol, m.p. 171°, when inserted at 155° (6° per min.). Titration with Karl Fischer reagent showed that not more than 0.15 $\pm$0.05% of water could be present.

Many crystallizations of the decahydrate of zirconium acetylacetonate (16) were required in order to remove the water. The crystallization temperature should not exceed 40°. Titration of the dehydrated form (m.p. 190°–191°) with Karl Fischer reagent showed that not more than 0.3$\pm$0.05% of water could be present. The sample used for dielectric constant determination was dried at 40° (20 mm.) for 24 hours before use. The density at 20° was found to be 1.415. According to combustion analysis the percentage of hydrogen in this sample is 5.68% as compared with 5.78% expected in $C_{20}H_{28}O_8Zr$.

Melting points have been corrected against reliable standards: Can. J. Technology, **34, 89 (1956).*

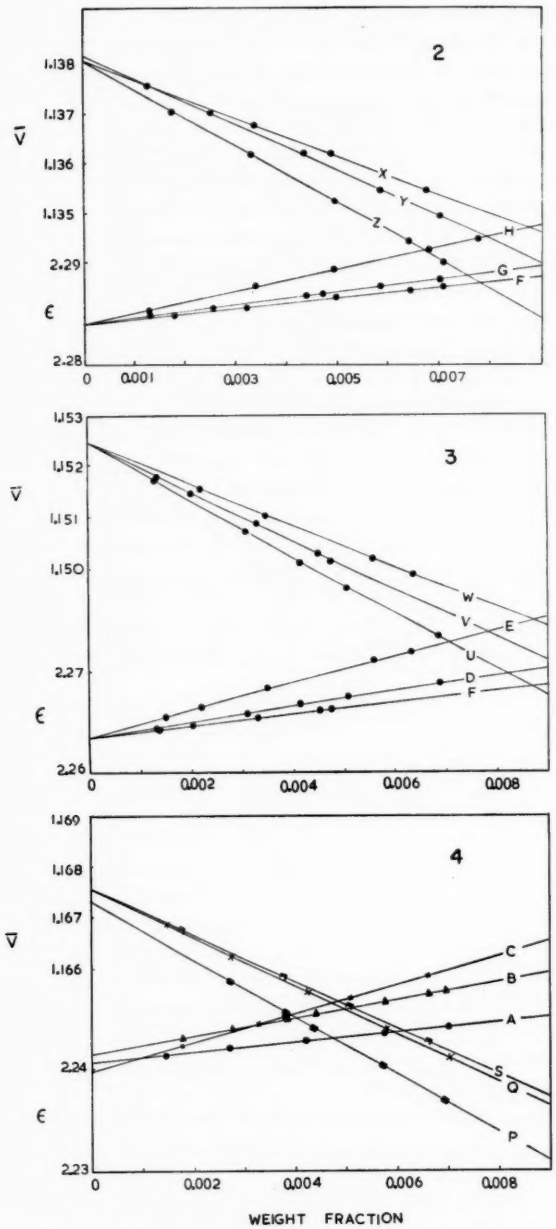

FIG. 2. Dielectric constants (*F*, *G*, *H*) and specific volumes (*Z*, *Y*, *X*) respectively for thorium acetylacetonate, *p*-dinitrobenzene, and zirconium acetylacetonate in benzene at 20°.

FIG. 3. Dielectric constants (*F*, *D*, *E*) and specific volumes (*V*, *U*, *W*) respectively for *p*-dinitrobenzene, thorium acetylacetone, and zirconium acetylacetonate in benzene at 30°.

FIG. 4. Dielectric constants (*A*, *B*, *C*) and specific volumes (*Q*, *P*, *S*) respectively for *p*-dinitrobenzene, thorium acetylacetonate, and zirconium acetylacetonate at 40°.

Density of Solids

These densities were determined by the air-displacement method described previously (17). The density determination of tetramethylcyclobutanedione was subject to error because of the significant vapor pressure of this substance. This error was evaluated and corrected after a series of analyses with samples varying in weight from 0.3 to 1.0 g.

Dielectric-Constant Measurements

The procedures and equipment described previously (1, 18) were used. A modification of the method for determination of ϵ for solids (17) involved a test capacitor built from a mild steel annulus 2.5 in. I.D. and 4 in. O.D. by 1 in. thick which was diametrically drilled for a Shardlow micrometer head at the top and a polystyrene-insulated "anvil" rigidly connected at the bottom to the ungrounded side of the VFO resonant circuit. Although this capacitor was very good for measurements at room temperature it was unsatisfactory at higher temperatures because of mechanical distortion, despite a prior normalization of the annular ring at liquid air temperatures.

The measurements in benzene solutions are shown in Figs. 2, 3, and 4. It may be seen that the dielectric constants and specific volumes are closely convergent at 20° (for benzene alone $\epsilon = 2.284$ and $\tilde{V} = 1.1380$) and at 30° (for benzene alone $\epsilon = 2.263$ and $\tilde{V} = 1.1525$) but at 40° (for benzene alone $\epsilon = 2.241$ and $\tilde{V} = 1.1675$) two batches of benzene were used. The lack of convergence at 40° actually is less serious than is apparent. In each experiment the extrapolation to the dielectric constant and the specific volume at zero concentration is within 0.0003 and 0.0001 respectively of the values for the pure solvent (1). The differences actually are due to variations in the residual capacity following disassembly of the test capacitor. At any rate the values for the most critical of these determinations (that of the *p*-dinitrobenzene) are very close to the dielectric

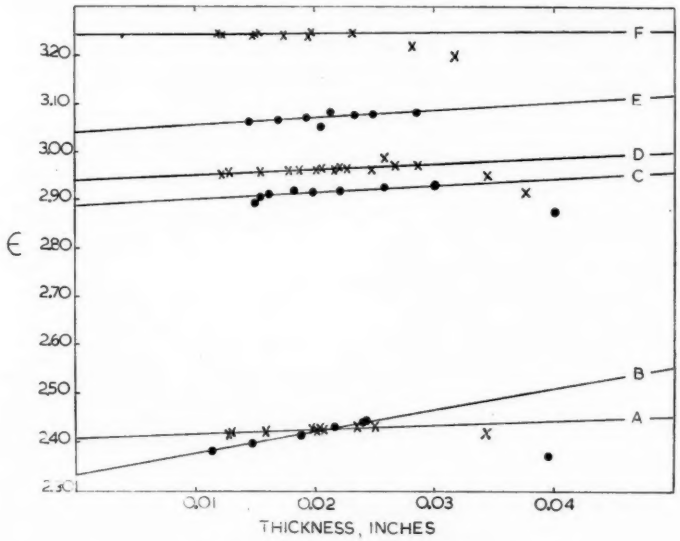

FIG. 5. Dielectric constants of solid:

A	*sym*-Tetramethylcyclobutanedione	D	Zirconium acetylacetonate
B	Koroseal	E	Thorium acetylacetonate
C	1,4-Dinitrobenzene	F	4,4-Dicyanobiphenyl

constant (2.2410) and the specific volume (1.1675) found for the pure solvent immediately after reassembly of the cell.

The dielectric constants of the solids, shown in Fig. 5, have been determined by use of gold amalgam. Included are data for the polyvinyl chloride sold under the trade name Koroseal. It is necessary to use 2% of this binder for satisfactory pelleting of some substances, such as the metal acetylacetonates marked † in Table I. In these instances a correction has been made by adding algebraically 2% of the difference between the dielectric constant of Koroseal and the mixture to the dielectric constant of the mixture.

It may be seen in Fig. 5 that the pellets of greatest thickness usually show dielectric constants lower than those falling on an extrapolatable line. It has been found by the flotation method that these pellets are less dense than those of lesser thickness. Since all pellets have been pressed at 12,000 lb. dead load, which is close to the yield-point of our dies, it is evident that thin pellets must be used for this method of determining distortion polarization.

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THE SYNTHESIS OF CRYPTOPLEURINE AND RELATED PHENANTHROQUINOLIZIDINES[1]

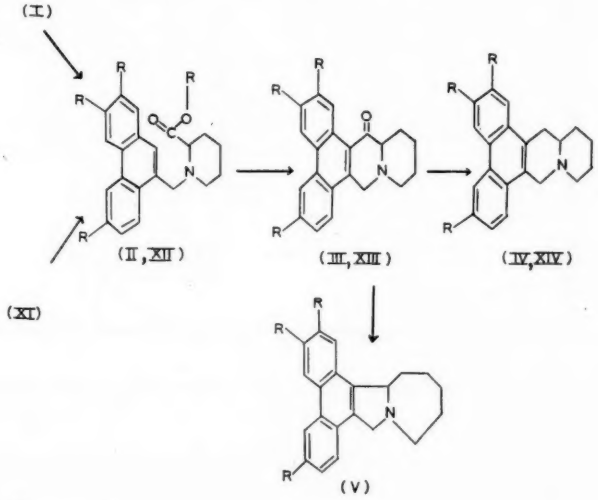
P. MARCHINI[2] AND B. BELLEAU

ABSTRACT

The synthesis of the alkaloid cryptopleurine has been accomplished by a sequence involving as the key step the cyclization of amino acid XII. It was established that the approach is applicable to the synthesis of simpler phenanthroquinolizidines such as IV. The biogenesis of the alkaloid is briefly discussed.

INTRODUCTION

The structure of the unusual alkaloid cryptopleurine (1) was deduced by Fridrichsons and Mathieson (2) by an X-ray investigation and its chemistry examined by Gellert (3). The remarkable physiological properties of this alkaloid have been described by de La Lande (1). Recently Bradsher and Berger (4) reported on a synthesis of cryptopleurine through the application of the general method already developed by Bradsher and Beavers (5, 6) for the synthesis of polycondensed quinolizines. In an independent investigation which was completed at the time Bradsher's report appeared, we accomplished the synthesis of cryptopleurine by a different route involving a series of well-characterized intermediates. Our approach differs from that of Bradsher's in that only reduced quinolizines are involved as intermediates (Chart I).



II, III, IV, V, R = H.
XII, XIII, XIV, R = CH_3O—.

CHART I.

In a model experiment, the synthesis of the phenanthroquinolizidone III was attempted through cyclization of the amino acid II, which was readily obtained from 9-chloromethylphenanthrene and methyl pipecolate followed by acid hydrolysis; this amino acid (II)

[1]*Manuscript received November 14, 1957.*
Contribution from the Department of Biochemistry, School of Medicine, Laval University, Quebec, Que.
[2]*Postdoctorate Fellow of the National Research Council of Canada (1956–1958).*

was heated to 100° in polyphosphoric acid whereupon smooth ring closure to the desired amino ketone (III) occurred in 50% yield. Optimum conditions for this conversion were studied and are given in the experimental section. Evidence for structure III is based on elemental analysis, the infrared absorption spectrum which includes a strong band at 1664 cm.$^{-1}$ characteristic of an aromatic ketone, and the ultraviolet spectrum (curve B, Fig. 1) which shows the characteristic secondary peak of 9-phenanthryl ketones at 320 mμ (7, 8). Reduction of the ketone (III) by the Huang-Minlon (9) procedure afforded

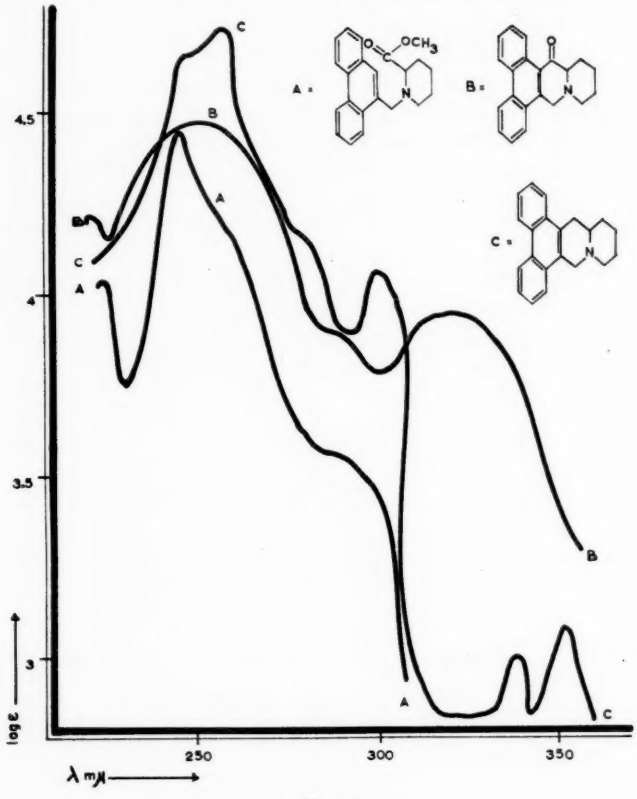


FIG. 1.

the desired phenanthroquinolizidine (IV) in high yield. Its ultraviolet absorption spectrum (curve C, Fig. 1) shows only the characteristic absorption bands of the phenanthrene nucleus, as expected. It is pertinent to note that Clemmensen reduction of the ketone (III) also produced a crystalline base in high yield of identical composition, but different from the one obtained by Wolff-Kishner reduction. Structure V is assigned to this product on the basis of the previous observations of Leonard and Wildman (10) on the reductive rearrangement of 1-quinolizidones.

With these results on hand, the synthesis of cryptopleurine itself could be considered, and a sequence of reactions also adopted by Bradsher (4) for the preparation of 9-bromomethyl-2,3,6-trimethoxyphenanthrene was carried out. Details of this synthesis are given in the experimental section and differ from Bradsher's synthesis in that only the

pure crystalline 9-chloromethyl derivative was used as a key intermediate. Reaction of the latter with methyl pipecolate followed by hydrolysis gave the amino acid (XII), which underwent smooth ring closure to 1-cryptopleurinone (XIII) when heated in polyphosphoric acid. The ultraviolet spectrum of the latter was recorded and as can be seen in Fig. 2 (curve E), the principal maxima exhibit a bathochromic shift with respect to the phenanthrene series and although the spectrum is similar to the one reported for

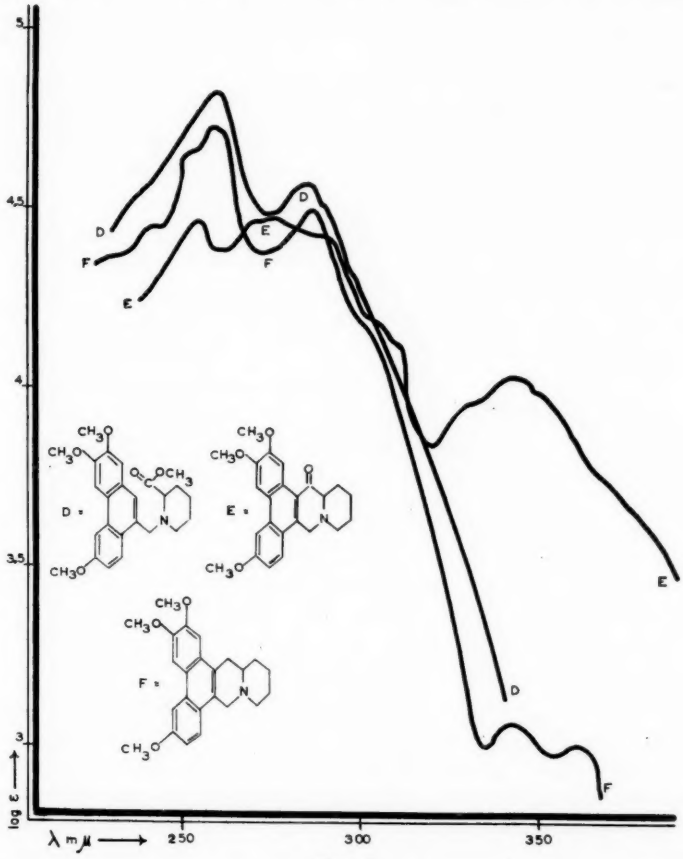


FIG. 2.

cryptopleurine, the peak at 345 mμ is of much greater intensity. Wolff-Kishner reduction of this ketone (XIII) gave rise to a mixture of phenolic compounds from which after treatment with diazomethane a small amount of crystalline material was obtained. The identity of the latter with cryptopleurine was ascertained by mixed melting point determination and by comparison of the infrared spectrum with an authentic specimen kindly provided by Dr. Bradsher. It should be noted that the spectrum was virtually superimposable on that of cryptopleurine except for the presence of a low-intensity band at 1700 cm.$^{-1}$ which is absent in the authentic specimen. It is most probable that this minor difference can be attributed to the presence of trace amounts of unchanged starting material in our sample or to deterioration of the latter on storage. The instability of

cryptopleurine has been commented upon before by Gellert (3). The small amount of material available precluded further purification or the preparation of the stable methiodide.

Additional proof of the identity of our material with cryptopleurine was obtained by comparison of the respective ultraviolet spectra, which proved to be identical in every respect (curve F, Fig. 2).

In view of Bradsher's recent report (4), no effort was made to improve the yield at the final stage of reduction although there can be little doubt that other procedures could be more successful.

The structure of cryptopleurine being of a novel type, it is of interest to attempt uncovering its biogenetical links with other classes of alkaloids. Robinson (11) suggested that the alkaloid originates from two tyrosine and one lysine unit. However, no mechanism was offered in support of this idea and we would like to suggest the scheme outlined in Chart II.

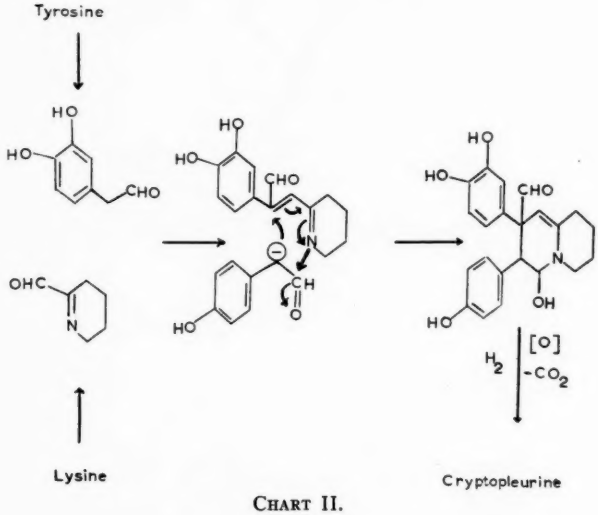


CHART II.

EXPERIMENTAL*

The spectra were determined with a Beckman spectrophotometer, Model DU, in 95% ethanol. Melting points are uncorrected and were obtained with a hot-stage microscope.

The pipecolic acid methyl ester was prepared by esterification of picolinic acid followed by hydrogenation in the presence of platinum oxide according to the procedure described by Tilford and co-workers (12).

The chloromethylphenanthrene was obtained by chloromethylation of phenanthrene as reported by Badger and co-workers (13).

Methyl N-(9-Phenanthrylmethyl)-pipecolate (1)

To a solution of 7 g. of methyl pipecolate in 150 ml. of methyl alcohol, containing 1.4 g. of potassium carbonate (freshly fused), 8.6 g. of 9-chloromethylphenanthrene was added at once. The mixture was then heated at 60°–70° and stirred for 12 hours. The suspension was evaporated almost to dryness and poured into water, and then extracted

**Microanalyses by Midwest Microlaboratories Inc., Indianapolis, Indiana, and Messrs. B. Girard and B. Mercier of our laboratories.*

with ether. The ethereal solution was washed with water, dried with sodium sulphate, and evaporated to a small volume. Treatment with dry hydrogen chloride gave a precipitate which after crystallization from acetone–ethyl acetate weighed 5 g., m.p. 177°–178°. λ_{max}: 255, 260, 289 mμ; log ϵ: 4.45, 4.40, 3.98 (curve A, Fig. 1). Calc. for $C_{22}H_{23}NO_2$.HCl.H_2O: C, 68.21; H, 6.70; N, 3.61. Found: C, 68.60; H, 6,92; N, 4.07.

Hydrolysis to the amino acid was accomplished by refluxing 5.5 g. of the ester (I) for 2 hours in 100 ml. of concentrated hydrochloric acid. After evaporation to half volume and cooling, 5.3 g. of crystalline material (II) was collected, m.p. 195°–200°. Calc. for $C_{21}H_{21}NO_2$.HCl: N, 3.9. Found: N, 3.8.

Phenanthro-(9,10;2,3)-1-quinolizidone (*III*)

To a solution of 10 g. of phosphorus pentoxide in 10 g. of sirupy phosphoric acid, 3 g. of the acid II was added at once. The mixture was heated to 100° for 6 hours with rapid stirring. After cooling the mixture was poured into ice-water, made alkaline with 50% sodium hydroxide solution, and extracted with chloroform.

The chloroform solution was washed with water, dried, and evaporated. The residue (III), weighing 1.4 g., crystallized from chloroform–methanol in light yellow prisms, m.p. 168°–169°. Calc. for $C_{21}H_{19}NO$: C, 83.74; H, 6.38; N, 4.64. Found: C, 83.46; H, 6.43; N, 4.62. The infrared spectrum showed (nujol mull) a strong band at 1664 cm.$^{-1}$. λ_{max}: 250, 260, 285, 320 mμ; log ϵ: 4.47, 4.42, 3.95, 3.95 (see Fig. 1, curve B).

Phenanthro-(9,10;2,3)-quinolizidine (*IV*)

To a solution of 0.6 g. of potassium hydroxide in 7 ml. ethylene glycol and 1 ml. hydrazine hydrate 0.5 g. of the ketone III was added. After refluxing for 1 hour (9), water was distilled, and distillation continued until the temperature of the vapors reached 195°; the mixture was then heated to 200° for 6 hours. The mixture was poured into water and extracted with ether. After evaporation of the solvent, the solid material was dissolved in hot ethanol and allowed to stand overnight: 0.3 g. of white needles was obtained, m.p. 169°–170° (sublimes at 155°). Calc. for $C_{21}H_{21}N$: C, 87.82; H, 7.31; N, 4.87. Found: C, 87.68; H, 7.52; N, 4.76. λ_{max}: 255, 260, 289, 330, 353 mμ; log ϵ: 4.48, 4.42, 3.90, 3.03, 3.07 (see Fig. 1, curve C).

3,4-Phenanthro-1-azabicyclo[0,3,5]decane (*V*)

To a refluxing solution of 0.4 g. of ketone III in 50 ml. of hydrochloric acid and water (3:1), 2.5 g. of zinc amalgam was added in small portions over a period of 4 hours. Every hour, 5 ml. of concentrated hydrochloric acid was added. After cooling, the solution was made alkaline and extracted with chloroform. The chloroform solution was evaporated and the residue dissolved in benzene. After filtration through a small column of basic alumina, the solution was evaporated to dryness. The solid material so obtained by crystallization from methanol gave 0.25 g. of white needles melting at 164°. Calc. for $C_{21}H_{21}N$: C, 87.82; H, 7.31; N, 4.87. Found: C, 87.46; H, 8.19; N, 5.05.

6-Nitro-3,4,4'-trimethoxy-α-phenylcinnamic Acid (*VI*)

Upon heating under reflux for 24 hours 58 g. of 6-nitroveratraldehyde (14) with 60 g. of homoanisic acid (15) in 300 ml. of acetic anhydride containing 5 g. of potassium acetate, 50 g. of crude product was obtained. After several crystallizations from acetic acid the m.p. was constant at 183°–184° (reported 185°–186°) (yield 38 g.).

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid (*VII*)

The preceding compound (37 g.) was dissolved in 112 ml. of 14% aqueous ammonia, and the resulting solution added at once to a hot solution of 228 g. of ferrous sulphate in

1 l. of 14% aqueous ammonia; the temperature was then maintained at 90° for a further 30 minutes. After cooling, careful neutralization of the mixture gave 30 g. of the corresponding amino acid. After several crystallizations from dilute ethanol, 25 g. of silky yellow crystals were obtained, m.p. 203°–204° (reported 206°–207°). Calc. for $C_{18}H_{19}NO_5$: N, 4.25%. Found: N, 4.23%.

This amino acid (23 g.) was suspended in 1400 ml. of water followed by the addition of 100 ml. of concentrated hydrochloric acid and 400 ml. dioxane. The mixture was cooled to 3°–5° and a solution of 9 g. of sodium nitrite in 100 ml. of water was added dropwise over a period of 2 hours, the temperature being kept below 5°. The clear, dark brown solution was then stirred for an additional 90 minutes.

After this time, 20 g. of activated copper bronze was added and stirring continued at room temperature for 24 hours. Evaporation *in vacuo* to half volume gave an amorphous precipitate which was collected by filtration and dissolved in chloroform. Evaporation of the solvent and crystallization of the residue from acetic acid afforded 12 g. of white crystalline material, m.p. 219°–220° (reported 222°). λ_{max}: 260, 280, 285 mμ; log ε: 4.58, 4.36, 4.33.

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid Methyl Ester (VIII)

The preceding acid (11.5 g.) (VIII) was heated under reflux for 2 hours in 250 ml. of methanol containing 15 ml. of sulphuric acid. The solution was then poured on ice and extracted with chloroform. Evaporation *in vacuo* left 10 g. of crude solid material. Chromatography on neutral alumina afforded in the petroleum ether eluate 5.4 g. of white crystals which crystallized from ethyl acetate – isopropyl alcohol, m.p. 156°–157°.* Calc. for $C_{19}H_{18}O_5$: C, 66.87; H, 5.52. Found: C, 66.76; H, 5.43. Extraction of the alumina with hot methanol gave 2 g. of white crystalline material, m.p. 85°–86°, which was not examined further.

2,3,6-Trimethoxy-9-phenanthrenemethanol (IX)

A solution of 5 g. of VIII in tetrahydrofuran was added dropwise with cooling to a suspension of 2.5 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was then heated under reflux for 90 minutes, the excess of hydride decomposed with ethyl acetate, and the mixture poured into water and extracted with chloroform–ether. Evaporation of the solvent gave 4.5 g. of white solid mass. Crystallization from ethanol gave 4 g. of white silky needles, m.p. 186° (reported 185°–187°).

2,3,6-Trimethoxy-9-chloromethylphenanthrene (X)

To a solution of 3.7 g. of IX in 170 ml. of anhydrous chloroform containing 2.2 ml. of pyridine was added dropwise 2.96 ml. of thionyl chloride at ice temperature. The reaction was brought to completion by heating at 40°–60° while stirring for 60 minutes. The mixture was then poured on ice, and the chloroform layer separated, washed with dilute bicarbonate solution, then with water, and dried. The residue obtained by evaporation of the solvent was crystallized from benzene and weighed 3.45 g., m.p. 150°–151°. Calc. for $C_{18}H_{17}O_3Cl$: C, 68.35; H, 5.35; Cl, 11.08. Found: C, 68.11; H, 5.56; Cl, 11.30.

Methyl 2,3,6-Trimethoxy-N-9-phenanthrylmethyl-pipecolate (XI)

A mixture of 3 g. of X and 6 g. of methyl pipecolate as free base† in 100 ml. of anhydrous toluene was heated under reflux with stirring for 20 hours.

The residue obtained after evaporation of the solvent was poured into water and the

**The ethyl ester of III prepared in an analogous way was crystallized from ethanol and melted at 137° (reported 136.5°–137°).*

†The base was prepared by treatment of the hydrochloride with sodium methoxide at room temperature for 12 hours and vacuum distillation, b.p. 88°/16 mm.

pH adjusted to 9 with alkali followed by extraction with chloroform. After it was washed with water, the solution was dried and evaporated to dryness to yield a solid which was dissolved in a small volume of ether. Treatment of this solution with dry hydrogen chloride gave a precipitate which crystallized from acetone – ethyl acetate. The weight of the hydrochloride was 4.7 g., m.p. 165°–167°. λ_{max}: 250, 260, 285 mμ; log ϵ: 4.67, 4.80, 4.55 (see Fig. 2, curve D). Calc. for $C_{25}H_{29}O_5N.HCl.\frac{1}{2}H_2O$: C, 64.10; H, 6.41; N, 3.00. Found: C, 63.49; H, 6.84; N, 3.03.

2,3,6-Trimethoxyphenanthro-(9,10;2,3)-1-quinolizidone (*XIII*)

The above ester (XI) was hydrolyzed by heating for 90 minutes in 80 ml. of hydrochloric acid. After cooling a microcrystalline material was collected and dried, and without further purification, 2.4 g. of this amino acid (XII) was added to a mixture of 10 g. of phosphorus pentoxide and 10 g. of phosphoric acid and the solution heated for $3\frac{1}{2}$ hours. After cooling, the violet mixture was slowly poured on ice, and after 50% potassium hydroxide solution had been added to pH 9, the mixture was extracted with chloroform.

The solution was washed with water, dried, and evaporated *in vacuo* under nitrogen to give 1 g. of a slightly yellow solid which crystallized from acetone–methanol as yellow prisms, m.p. 154.5°–155°. λ_{max}: 255, 270, 290, 310, 345 mμ; log ϵ: 4.42, 4.51, 4.40, 4.02, 4.01 (see Fig. 2, curve E). Calc. for $C_{24}H_{25}O_4N$: C, 73.66; H, 6.39. Found: C, 73.87; H, 6.84.

2,3,6-Trimethoxyphenanthro-(9,10;2,3)-quinolizidine (*XIV*)

The reduction of 0.45 g. of XIII was effected as described above in the case of IV except that the reaction was carried out under nitrogen. The crude reaction product was chromatographed on basic alumina but no pure substance could be obtained from the various eluates. A ferric chloride test was strongly positive for all of the main fractions; a 0.25 g. portion of the brown waxy material was therefore treated in methanol–ether with a large excess of diazomethane and allowed to stand overnight.

Evaporation of the solvent *in vacuo* gave an oil which was dissolved in ether and extracted with dilute hydrochloric acid. Neutralization of the acidic solution gave a precipitate which was extracted with ether. After evaporation of the solvent, the residue was dissolved in a small volume of acetone and allowed to stand at −10°. The solution slowly deposited 5 mg. of light yellow needles which after several recrystallizations had m.p. 199°–201° (reported 197°–198° (3), 199°–200° (4)). Mixture with an authentic specimen of cryptopleurine gave no depression of the melting point. λ_{max}: 258, 286, 345, 358 mμ; log ϵ, 4.70, 4.47, 3.12, 2.97.

The infrared spectrum was recorded with a Baird double-beam instrument using the KBr pellet technique. The spectrum was identical to that of cryptopleurine except for the presence of a low-intensity band at 1700 cm.$^{-1}$.

ACKNOWLEDGMENTS

We express our gratitude to Dr. C. K. Bradsher for supplying an authentic specimen of cryptopleurine and to Dr. H. Hooper of Bristol Laboratories Inc. for the infrared determinations. We also express our thanks to the National Research Council of Canada for a fellowship to one of us (P.M.) and for financial assistance.

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NOTES

THE REDUCTION OF SOME HALOGENATED COMPOUNDS BY CHROMOUS CHLORIDE

F. A. L. Anet and Elaine Isabelle

Reduction of annotinine chlorohydrin by chromous chloride gave two compounds (1, 2), (*a*) "hydroxylactone" and (*b*) "unsaturated lactone A", neither of which was the "normal" reduction product which would be formed by replacement of chlorine by hydrogen. Anet and Marion (2) suggested that these two compounds were formed by 1,2-elimination, analogous to the reduction of *vic*-dibromides to alkenes (3), and involving a chlorine atom and a β-nitrogen atom in the case of the "hydroxylactone", and a chlorine atom and a β-hydroxyl group in the case of the "unsaturated lactone A".

In order to obtain analogies for the reduction of annotinine chlorohydrin, whose structure is now firmly established (4, 5), we have studied the chromous chloride reduction of some simple β-halogenated alcohols and amines. 2-Chloroethanol was not reduced under the conditions used. 2-Bromoethanol was reduced slowly and gave 20% ethylene, isolated as the dibromide, but a considerable amount of starting product was hydrolyzed. 2-Bromoethylamine was reduced to a mixture of ethylamine, ammonia, and ethylene. In this case the "normal" reduction product, formed by simple replacement of halogen by hydrogen, was a reaction product, whereas the "normal" reduction product of annotinine chlorohydrin has not been observed. Nevertheless, the same type of reduction was found in the simple model compounds as occurred in annotinine chlorohydrin.

EXPERIMENTAL

Preparation of Aqueous Chromous Chloride Solution

Chromic chloride hexahydrate (100 g.) was dissolved in 15% hydrochloric acid (600 ml.) and reduced with amalgamated mossy zinc (100 g.) under an atmosphere of nitrogen. An apparatus of the type suggested by Lingane and Pecsok (6) was used for the reduction and storage of the reagent.

Reduction of 2-Chloroethanol

2-Chloroethanol (0.1 mole) was treated with chromous chloride solution (0.2 mole) under an atmosphere of nitrogen. The reaction mixture was heated under reflux for 3 hours and all escaping vapors were passed through an all-glass system to a series of bromine traps. During this time there was no evidence of any evolution of gas and no visible loss of blue color in the chromous solution. The bromine in the traps on being worked up yielded no trace of ethylene bromide, and distillation of the reaction mixture yielded no ethanol.

Reduction of 2-Bromoethanol

2-Bromoethanol (0.05 mole) was reduced with chromous chloride solution (*ca.* 0.1 mole). The mixture was heated under reflux in an atmosphere of nitrogen for 3 hours during the last half-hour of which a slow stream of nitrogen was allowed to pass through the system to entrain any ethylene produced and carry it to the bromide absorption traps. A trap containing water was placed before the bromide traps to scrub out any ethanol entrained.

The dibromide collected was washed with water and sodium carbonate solution until colorless. The dibromide layer was separated, the washings extracted with ether, and the combined extract, after being dried over calcium chloride, yielded on distillation 2.1 g. of pure ethylene dibromide (22% yield).

A Schotten–Baumann reaction modified (7) to detect small quantities of ethanol in aqueous solution failed to produce any ethanol derivative either from the water trap or from the initial distillate of the reaction mixture.

Control on Hydrolysis of 2-Bromoethanol

2-Bromoethanol (5 g.) was heated under reflux with 15% hydrochloric acid (30 ml.) for 3 hours. The mixture was salted out with sodium chloride and extracted five times with small quantities of ether. The ether extracts were combined, dried over magnesium sulphate, and evaporated, leaving slightly less than 1 g. of residual oil.

Reduction of 2-Bromoethylamine Hydrobromide

2-Bromoethylamine hydrobromide (0.05 mole) was reduced under nitrogen with chromous chloride solution (0.1 mole) by heating under reflux for 3 hours. The ethylene evolved was converted to the dibromide as described above, yield 4.6 g. (49%).

The residue was rendered alkaline with sodium hydroxide and steam-distilled into a dilute hydrochloric acid solution. The acidic solution was evaporated to dryness, yielding 3.49 g. of white solid. By fractional crystallization from ethanol the ammonium chloride was separated from ethylamine hydrochloride, m.p. 96°–98°, which did not depress the melting point of a known sample of ethylamine hydrochloride, and formed a benzoyl derivative, m.p. 70° (lit. m.p. 71° (8)). The ammonium chloride was estimated to comprise approximately 60% of the mixture, the ethylamine hydrochloride 40%.

ACKNOWLEDGMENT

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OTTAWA, CANADA.

GAS–LIQUID PARTITION CHROMATOGRAPHY OF ORGANIC SULPHUR COMPOUNDS[1]

C. H. AMBERG

To assist in the identification of organic sulphur compounds in cracked distillates derived from Canadian crudes the relative elution times of a number of such compounds

[1]*Issued as N.R.C. No. 4615.*

have been measured by gas–liquid partition chromatography (GLPC). The results are recorded in the accompanying table. Few references to the separation of organic sulphur compounds by GLPC have so far appeared in the literature (1, 2, 3).

EXPERIMENTAL

The samples were eluted with nitrogen from glass columns containing tricresyl phosphate supported on Johns-Manville C-22 firebrick in the ratio 2:5 w/w. Particle sizes were 35–80 mesh for columns up to 12 ft. in length and 35–60 mesh for 18-ft. columns. The injection system consisted of a heated chamber at the column head; inside the chamber were two disks of 60-mesh stainless-steel gauze from which the liquid was flashed on to the column packing after having been introduced in the usual manner by a syringe through a self-sealing rubber cap. Flow rates were in the range 25–40 ml./min. with 1 atmosphere pressure at the column head and pressures down to 5 mm. Hg at the outlet. A thermal conductivity gauge served as monitor for the effluent stream; both the detector and reference elements were placed at the column outlet with liquid nitrogen traps interposed between the two. The traps were designed to fit directly onto a mass spectrometer. In this manner the mass spectra of separate eluate fractions could be determined.

The standard liquids indicated in Table I were benzene (B), toluene (T), and ethyl-

TABLE I

RELATIVE ELUTION TIMES OF ORGANIC SULPHUR COMPOUNDS

Compound	Column temperature, °C.	Standard liquid	Relative elution time
Mercaptans			
2-Propanethiol	85	B	0.36_2
2-Methyl-2-propanethiol	85	B	0.41_3
1-Propanethiol	85	B	0.58_1
2-Methyl-1-propanethiol	85	B	0.92
3-Methyl-1-butanethiol	85	B	1.97
1-Butanethiol	101	T	0.58_9
1-Pentanethiol	101	T	1.20
1-Hexanethiol	100	T	2.32
Sulphides			
Thiapropane	85	T	0.137
2-Thiabutane	85	T	0.272
3-Thiapentane	85	T	0.48_9
4-Thiaheptane	85	T	1.77
Thiacyclopentane	85	T	1.55
	94	T	1.52
Alkylthiophenes			
Thiophene	65	B	1.38
	85	B	1.42
2-Methylthiophene	85	T	1.18
	94	T	1.16
3-Methylthiophene	85	T	1.35
	94	T	1.33
2-Ethylthiophene	85	T	2.18
3-Ethylthiophene	85	T	2.72
2,5-Dimethylthiophene	85	T	2.11
2,4-Dimethylthiophene	85	T	2.51
2,3-Dimethylthiophene	85	T	2.82
3,4-Dimethylthiophene*	84	E	1.76
2-Methyl-5-ethylthiophene*	84	E	2.2
2,3,5-Trimethylthiophene*	85	E	2.7

benzene (E). All elution times were corrected by subtracting that of hydrogen for the same operating conditions, thus allowing for "dead volume". Compounds marked with an asterisk have been identified in petroleum distillates by boiling range and mass spectrometry only; they have so far not been confirmed by measuring the elution time of the pure compound.

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